Monitoring the Internet for Nootropic Substances Available to Australian Consumers

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Statement of Sources

I declare that this research report is my own work and that, to the best of my knowledge and belief, it does not contain material from published sources without proper acknowledgement, nor does it contain material which has been accepted for the award of any other higher degree or graduate diploma in any university.

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'Clear eyes, full hearts, can't lose.'

-The Dillon Panthers

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Abstract

There is a historical interest in improving cognitive performance for individuals in fields such as academia. Nootropics, also known as smart drugs, are increasingly being used by individuals to obtain desirable cognitive benefits. Research has focused on investigating the potential benefits of nootropics through animal studies, however there is limited knowledge regarding the potential adverse side effects of these substances in humans. An online, active community of nootropic consumers have provided consumer experiences and advice for new consumers, to aid in the navigation of the vast nootropic online market. The current two-part study aimed to firstly monitor the nootropic market available to the Australian consumer, and secondly, to provide a narrative review of the top ten most commonly available nootropics. The 12-month monitoring revealed a vast, relatively stable nootropic marketplace. Adrafinil, Alpha GPC, Aniracetam, Noopept, Oxiracetam, Phenibut, Centrophenoxine, L-theanine, Phenylpiracetam, and Paramiracetam were identified as the ten most common nootropics on the market and were the focus of the narrative review. The second study revealed several psychological (e.g., anxiety and low mood) and other (e.g., physical pain and sleep difficulties) side effects of the commonly used nootropics. The current study was limited in that the nootropics were not purchased to ensure product availability, and by the validity and reliability of consumer reports. It is advisable that clinicians increase their understanding of the potential harms nootropics may have on consumers. Future research is required to further explore and validate these side effects.

The human pursuit of using technology to maximize performance dates back to the stone age (Buyx, 2015). In more recent history, humans have developed medical technology that not only addresses illness and disease, but also focuses on improving what is considered normal human performance (Buyx, 2015; Cavanna, 2015; Kramer, 1993). Specifically, there has been an interest in improving cognitive performance for benefits in fields that rely heavily on cognitive ability (e.g., working memory, attention, etc.), such as academia, e-sports (i.e. competitive video gaming) and computer coding (Holden, Rodenberg, & Kaburakis, 2017; Talih & Ajaltouni, 2015). Previously, this type of technology was labelled as 'cosmetic psychopharmacology' (Kramer, 1993). However, more recently, a shift in nomenclature has occurred, with terms such as 'smart drugs' and 'nootropics' being more commonplace (Buyx, 2015; Talih & Ajaltouni, 2015). Buyx (2015) notes that the term 'smart drug' is problematic due to the implicit message that these substances are smart in their action, or that people who take them are inherently smart. These cognitive enhancing drugs have also generated significant media attention due to their potential for increased performance, and are known by many different names (e.g., nootropics, cognitive enhancers, brain supplements, neuroenhancements and smart pills). For the purpose of the current study, the term nootropics will be used to describe these cognitive enhancing substances, however it is noted that these terms are interchangeable.

There is a growing body of literature that suggests there has been an increase in the use of nootropics (Hupli, Didziokaite, & Ydema, 2016; Mazanov, Dunn, Connor, & Fielding, 2013), which has attracted investigation from a diverse range of professionals (Dowling et al., 2016). In addition to increases in current empirical literature, media coverage has also accumulated. Partridge, Bell, Lucke, Yeates, and Hall's (2011)

examination of media reports, revealed that 66% of the media coverage on nootropic drugs referred to academic literature, with a tendency to under-report potential side effects. As both the study and public interest for nootropics grows, so do the markets that provide these substances to consumers. In 2015, the global market for nootropics was valued at $1,346.5 million USD with numbers expected to increase (Acute Market Reports, 2016). In line with the growing interest in media coverage and scientific literature, the current study aims to contribute to the understanding of nootropics.

Types and Use of Nootropics

Nootropic drugs claim to improve specific aspects of cognition such as attention, alertness, memory, and cognitive control (Buyx, 2015; Holden et al., 2017; Talih & Ajaltouni, 2015). Research on cognitive improvements has predominately focused on animal studies, with scarce research involving human samples (Ahmad et al., 2017). Notably, there may be a desire for consumers to be on the cutting edge of cognitive enhancement, which may in turn result in disregarding the limitations of the methods used in supportive research studies. The process whereby researchers do not study a new drug in humans until it has undergone safety testing in animal samples, creates an over reliance on animal literature for consumers who want to be on the cutting edge. Specifically, in Australia, new medications undergo a four-phase clinical trial process (see Table 1; Australian Clinical Trails, 2015). The overarching aim of this process is to ensure efficacy of the substance to provide expected outcomes, while identifying and minimizing risk to human consumers. Nootropic substances are often still in *phase zero* and have not been tested as vigorously.

Table 1

Summary of the Phases of Clinical Trials in Australia (Australian Clinical Trials, 2015)

Clinical Phase	Required Sample	Expected Outcome
Phase Zero Trials (exploratory studies/pilot studies)	Testing medication in its infancy across animal and very small (n = 1-2) human samples.	To identify how the body may respond to the experimental medication.
Phase I Clinical Trial	Testing new medications/ interventions in a small sample of human subjects (n = 20-30).	To identify safe dosage levels and potential side effects.
Phase II Clinical Trial	Testing medications/ interventions from Phase I in a larger sample of human subjects (n = 100-300).	Further identify potential side effects in a more representative sample of consumers.
Phase III Clinical Trial	Testing medications/ interventions for efficacy when compared to already ratified medications or interventions in a large group of humans (approx. n = 300-3000).	To identify efficacy of medication as well as continuing to explore side effects.
Phase IV Clinical Trial	Completed when the medication has been marketed and is available to the consumer outside of clinical trials.	Monitor efficacy of medication in the general population of human consumers.

Another challenge for nootropic research is in regard to the classification of nootropic substances. Due to the large number of substances that fall under the umbrella term of nootropics, there has been difficulty in the classification and formal categorisation of nootropics (Ragan, Bard, & Singh, 2013). Prescription pharmaceuticals (e.g., modafinil and methylphenidate) are often prescribed to address a cognitive concern due to an underlying illness or psychiatric diagnosis. One example is modafinil, a pharmaceutical commonly used in the treatment of narcolepsy and more recently for a range of psychiatric, neurological, and medical illnesses (e.g., depression, multiple

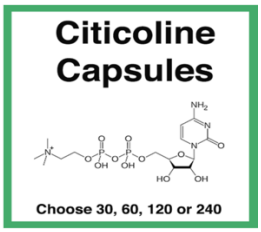
sclerosis and Lewy bodies dementia; Capouch, Farlow, & Brosch, 2018; Kaufman, Menza, & Fitzsimmons, 2002; Myrick, Malcom, Taylor, & LaRowe, 2004; Taylor & Russo, 2000; Zifko, Rupp, Schwarz, Zipko, & Maida, 2002). Recently, there has been an increase in the use of prescription pharmaceuticals for off-label purposes (Buyx, 2015). Off-label purposes are described as the use of pharmaceuticals outside of their original intention, for example using antidepressants for the treatment of pain symptoms. Individuals are using medications such as modafinil for the off-label purpose of cognitive benefits (Buyx, 2015; Chatterjee, 2006; Myrick et al., 2004). Synthetic compounds have also become more popular and are increasingly being formulated to enhance cognition (e.g., Precetatam; Gouliaev, & Senning, 1994). Additionally, other commonly known substances such as caffeine and naturally occurring substances such as Ginkgo Biloba, Rhodiola Rosea, and Ginseng, are being sought by consumers to improve areas of cognition (Suliman et al., 2016; Tabassum, Rasool, Malik, & Ahmad, 2012). Nootropic blends (i.e. more than one substance combined), both natural and synthetic, have also emerged with claims of improved cognition (Cadenhove, Sambeth, Sharma, Woo, & Blokland, 2017).

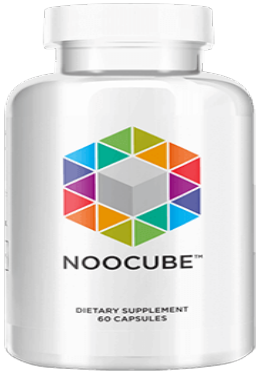
Upon examining the current literature, nootropics appear to come from a variety of sources (e.g., prescription pharmaceuticals, synthetic compounds, and naturally occurring substances), largely dependent on their anticipated purpose. Importantly, Ragan et al. (2013) indicated that no concrete classification for nootropic substances exists. The current study will classify nootropics within three broad categories including 1) specified (i.e. substances that make up the nootropic are clearly labelled), 2) unspecified (i.e. substances are not clearly labelled), and 3) whether the specified/unspecified substance is a blend (i.e. more than one substance combined).

Table 2 provides examples of nootropics available online, descriptions of the product from vendors, and how they would be classified under the current study's approach.

Table 2

Examples of Current Nootropics and Classification

Nootropic Name	Image	Advertised Description	Specified/ Unspecified	Blend (Yes/No)
Adrafinil	 (Nootropicsdepot, September 29, 2017)	"*Nootropics Depot offers 5g, 15g or 30g jars of Adrafinil powder. Nootropics Depot's Adrafinil has been lab-tested and verified for both product purity and identity.*" (Nootropicsdepot, September 29, 2017)	Specified	No
Armodafinil	 (ModaPharma, September 29, 2017)	"*Armodafinil is a more recent form of Modafinil, consisting only of the (−)-(R)-enantiomer. Compared to Modafinil, Armodafinil has a longer duration of action (10 to 12 hours vs 6 to 8 hours), with a more rapid onset of action.*" (ModaPharma, September 29, 2017)	Specified	No
Citicoline	 (Totalnootropics, September 29, 2017)	"*Main benefits, supports your focus and attention. Supports your memory.*" (Totalnootropics, September 29, 2017)	Specified	No

Nootropic Name	Image	Advertised Description	Specified/ Unspecified	Blend (Yes/No)
Ginkgo Biloba	 (Iherb, September 29, 2017)	"*Our Ginkgo Biloba Extract is the finest quality available worldwide. Scientific research has demonstrated that Ginkgo Biloba Extract has powerful free radical scavenging activity in vitro studies.*" (Iherb, September 29, 2017)	Specified	No
Modafinil	 (ModaPharma, September 29, 2017)	"*Modafinil is a eugeroic drug or wakefulness-promoting agent. Prescribed around the world for chronic fatigue syndrome, obstructive, sleep apnea, shift-work, sleep disorder, ADHD and Narcolepsy.*" (ModaPharma, September 29, 2017)	Specified	No
Noocube	 (Noocube, September 29, 2017)	"*NooCube is a synergistic blend of nootropics which helps support and enhance your focus, mental speed and memory. Safely and effectively improve your cognitive functioning with this powerful blend of vitamins, amino acids and other essential building blocks for a healthy, well-functioning brain.*" (Noocube, September 29, 2017)	Umspecified	Yes

Nootropic Name	Image	Advertised Description	Specified/ Unspecified	Blend (Yes/No)
Nootroo	 (Nootroo, September 29, 2017)	"*Nootroo's tagline is The Gold Standard in Nootropic, because of our dedication to creating the best nootropics possible, by using only the purest, most-effective ingredients and never cutting any corners.*" (Nootroo, September 29, 2017)	Unspecified	Yes
Piracetam	 (Nootropicsdepot, September 29, 2017)	"*Piracetam is a nootropic compound in the 'racetam' family that is structurally similar to the neurotransmitter GABA (though it does not function in the same way). As the 'parent molecule' of the racetam family, Piracetam was first synthesized in 1964. All other racetams, including others like Aniracetam, share the same 2-pyrrolidone base structure*" (Nootropicsdepot, September 29, 2017)	Specified	No
Rhodiola	 (Iherb, September 29, 2017)	"*generally known as an 'adaptogen', a term which refers to any agent possessing the ability to support the body's natural capacity to adapt to life's changing conditions.*" (Iherb, September 29, 2017)	Specified	No

Despite the value of nootropics on the market, evidence of their effectiveness for improving human cognition is scarce, and information regarding their potential for adverse side effects is limited. Additionally, the research that does exist is criticised based on factors such as small sample sizes and poor representativeness of samples (Ahmad et al., 2017; Buyx, 2015; Cadenhove, 2017; Carton et al., 2018; Smith, & Farah, 2011). Foreseeably, there is a risk to consumers, as the size of the nootropics market is large and there is a lack of reliable information regarding these substances, making it difficult to be an informed consumer. Despite the growing nootropics marketplace, there is a gap in the literature in regard to the various types of nootropics that are available and being readily purchased by consumers. The current study aims to address this gap by monitoring the online nootropic marketplace, based on previously used substance monitoring systems (Bruno, Poesiat, & Matthews, 2013; Psychonaut Web Mapping Research Group, 2010).

Prevalence of Nootropic Use

Existing literature has indicated academics, students, scientists, pilots, and gamers, are populations likely to use nootropics to enhance performance in their respective fields (Buyx, 2015; Ragan et al., 2013; Savulich et al., 2017; Van Zyl et al., 2017). The media however, has been noted to exaggerate the use of nootropics, often reporting their use as ‘common place’ amongst students (Buyx, 2015; Ragan et al., 2013). Ragan et al. (2013) reviewed nootropic prevalence literature, reporting nootropic use rates between 1% - 33% internationally. The samples differed substantially in regard to country (e.g., Germany, United Kingdom, Demark, Belgium and Iran), population (e.g., medical students, staff and employees), and nootropic studied (e.g., modafinil, unspecified stimulants, caffeine and methylphenidate), emphasising the difficulty in

obtaining reliable and meaningful prevalence data. A review of the misuse of medication studies by Wilens et al. (2008) identified that five to nine per cent of US school age students, and five to 35% of US university students, reported using non-prescribed cognitive enhancement medication originally prescribed for individuals with Attention-Deficit Hyperactivity Disorder (ADHD) in the prior year.

Ragan et al. (2013) suggests a lack of concrete prevalence data exists due to inconsistency regarding methodologies and samples. Furthermore, little is known about the prevalence of nootropic use outside of student populations in the US (Smith & Farah, 2011). There is a trend that individuals are using nootropics at an increasing rate, supporting the media's portrayal emphasising more prevalent use of nootropics in populations that are being most heavily researched (i.e. student populations).

Nootropic Use in Australia

Limited studies have examined the prevalence of nootropic use in Australia. Riddell, Jensen, and Carter (2017) reported that in a national sample of 633 Australian university students, 51% had used illegal and legal nootropics, at least once in their lifetime, with the intention of achieving cognitive benefits. Furthermore, findings suggested relatively low use of illicit drugs compared to the use of prescription nootropics, with modafinil being the most commonly used nootropic (Riddell et al., 2017). Furthermore, only an estimated 6.3% of students reported using a prescription nootropic substance (e.g., beta-blocker, dexamphetamine, modafinil) at least once, with modafinil being the substance most frequently used (Riddell, 2017). The use of non-prescription substances (e.g., caffeine pills, energy drinks and coffee) for cognitive enhancements was more common, with 50.6% of students using these at least once (Riddell, 2017). Illicit substances were less commonly used for cognitive enhancement,

with approximately two per cent of students using these substances (Riddell, 2017). Conversely, the study indicated university students more commonly used legal enhancers (e.g., caffeine pills and energy drinks), in an attempt to experience cognitive benefits. In a 2015 Australian cross-sectional sample (n = 763) that monitored the use of psychostimulant and related drug use (Nelson & Lenton, 2017), 18.2% of frequent psychostimulant users (e.g., ecstasy and related drugs) had used nootropics in the previous six months. Dexamphetamine, methylphenidate, modafinil, and racetams (e.g. Aniracetam, Oxiracetam, Phenylpiracetam, and Pramiracetam) were the most commonly reported nootropic substances used (Nelson & Lenton, 2017). Nelson and Lenton (2017) noted that being a university student was a predictor for both over-the-counter nootropic and illicit nootropic use in this sample.

Similar to international consumers, Australian consumers have reported using nootropics to improve various areas of cognition, specifically concentration, academic performance, motivation for study, and increased rate of task completion (Nelson & Lenton, 2017). Jensen, Forlini, Partridge, and Hall (2016) noted that Australian students are more likely to use nootropics near task deadlines, where students were unable to use non-substance related coping strategies (i.e. emotional coping) to manage their workloads.

A substantial proportion of illicit drug consumers who also use nootropics, source their nootropics from online vendors, particularly those who reported consuming racetams (Nelson & Lenton, 2017). In a recent media article, McNeilage (2018) noted that ten Australian high school students were admitted to hospital due to intoxication (i.e. dizziness and nausea) after consuming Phenibut, a nootropic purchased online. These current insights into nootropic use in Australian consumers, highlight the

importance of expanding the literature to provide up to date information regarding the potential side effects of nootropic use.

Reddit and Nootropics

One of the factors that may have contributed to the expansion of nootropics use is the online community. Reddit is the largest online forum, described as 'the front page of the Internet' (Squier & Fisk, 2013), and has a sub-forum dedicated to nootropics ('r/nootropics'). Squier and Fisk (2013) provided a commentary on the importance of the Reddit community in allowing new consumers to access r/nootropics to obtain information regarding the common uses, distribution, and education of nootropics. The r/nootropics community was described as medium sized (approximately 25,000 subscribers) in 2013 (Squier & Fisk, 2013). In 2018, this number increased to 143,000 subscribers (Reddit, June 2018).

Often subscribers post their first-hand experiences with nootropics, ask questions, post research articles, review sellers of nootropics ('vendors'), and engage in other nootropic-based discussion. Squier and Fisk (2013) suggest that the Reddit community have allowed for first time users of nootropics to have an accessible source of information from past users. It is noted by Squier and Fisk (2013) that the r/nootropics community have become critical of the empirical literature, as the literature has not caught up with consumer reports of cognitive benefits. This is foreseeably dangerous, as if consumers are focused upon subjective reports of cognitive benefits rather than potential side effects, there is an unknown possibility for adverse outcomes. Specifically, the enthusiastic but anecdotal nature of these reports, combined with the absence of a clear guide to benefits and risks, increases the risk to consumers. Furthermore, there is a need for future research to explore these gaps in the literature to

inform consumers, to reduce the misuse of nootropics given the effects are currently unclear.

To the author's knowledge, the literature has not yet examined public forum user reports for potential side effects of widely available nootropics. This is a method that has been adopted previously in consumers of novel illicit substances (e.g., Poesiat & Bruno, 2013). Therefore, as there is a large public forum in which nootropic consumers post their experience, these forums may be useful in gathering and reviewing the experienced side effects of these substances.

Current Challenges and Concerns Regarding Nootropics

With the use of nootropic drugs becoming more widespread, ethical issues have arisen. Cakic (2009) noted the similarity of nootropic drug use in academia to performance enhancing drugs in competitive sport. There are concerns that the use of nootropics will become generalised and this will place non-users at a disadvantage (Cakic, 2009). This trend may in turn force non-users to use nootropics to keep up with students using nootropics. E-sports (i.e. competitive video gaming) has faced similar challenges with athletes (i.e. professional gamers) using nootropics (e.g., modafinil, methylphenidate, and dextroamphetamine) to gain a competitive gaming advantage (Holden, Kaburakis, & Tweedie, 2018). In an attempt to restrict the effect of nootropics in e-sports, policy has been discussed and implemented to ensure competitions are fair and not subjected to doping (Holden et al., 2017; Holden et al., 2018). As individuals are using medications that have not been prescribed to them (e.g., dexamphetamine) or substances in which there has been no human safety checking, concerns have accordingly been raised. These concerns include the potential risks of adverse events as a result of the consumption of these substances given the lack of medical monitoring, or

oversight by the consumer. Further research and education for potential consumers has been highlighted as a key clinical consideration to be addressed (Wilens et al., 2008). In addition to concerns regarding the medical implications for the consumption of unprescribed medications, concerns associated with the possible mental health effects of nootropic drugs have also been identified. With the rise of nootropic use, there are concerns around how to regulate, provide relevant information (e.g., dosage, evidence-based risks, and benefits), and manage the legal supply of nootropics (Cakic, 2006; Farah et al., 2004; Ragan et al., 2013).

Mental Health and Nootropics

Talih and Ajaltouni (2015) aimed to raise awareness to physicians, psychologists, psychiatrists, and other health professionals, on the potential negative effects of nootropic drugs. Their study revealed commonly used nootropics (e.g., Armodafilil, Citicoline, Piracetam, Amapakines), their side effects (e.g., headaches, tremors, diarrhoea, etc.), and their desired psychotropic effect (e.g., wakefulness, memory, cognition, etc.). They also presented four case studies of young, American adults who had used such nootropics. The first case study described a 19-year-old male that had been treating his ADHD and depression with Citicoline, a nootropic he had purchased online. The use of this drug resulted in the individual being admitted to a psychiatric hospital with psychosis and paranoia with self-harming behaviours. The second case study described a 24-year-old male presenting with agitation, anxiety, and hypersomnia, related to Cerebrolysin use, a nootropic drug he had purchased to enhance cognitive performance. The third case study described a 28-year-old female who presented to the emergency room with insomnia, anxiety, and panic attacks. This individual admitted to using Armodafinil, a nootropic drug she had purchased online to

help with the academic stresses of university. The final case study noted a 17-year-old male who was admitted to hospital due to elevated levels of restlessness and paranoia. The patient disclosed the use of Piracetam, a nootropic purchased online, which the consumer believed was safe to use as it was advertised as a “natural remedy”. In a further case study of nootropic use, Wong, Little, Caldicott, Easton, and Greene (2015) described a 43-year-old male who had consumed Phenibut, a nootropic that has become widely available online, to self-treat insomnia. The male presented to the emergency room with increased agitation and involuntary muscle contractions. Due to the severity of his symptoms he had to be stabilised in the intensive care unit. Historical information identified that the individual had previously been admitted to the hospital following Phenibut use on three separate occasions. Wong et al. (2015) noted increasing concerns around nootropic drugs being available online and their unknown physical and mental health side effects. These case studies suggest that there are potential mental health risks for nootropic use (Talih & Ajaltouni, 2015; Wong et al., 2015). Talih and Ajaltouni (2015) suggested that it is particularly important for mental healthcare professionals to be aware of nootropic drugs and their potential dangers. This is important so that healthcare professionals can consider the side effects during assessment, and to understand their potential dangers and how this may impact treatment progression for a client using nootropics.

The research currently available suggests nootropic consumers have experienced negative side effects as a result of their nootropic use (Nelson & Lenton, 2017; Ragan et al., 2012; Talih & Ajaltouni, 2015). However, there appears to be a lack of large-scale studies investigating such effects, and current research has largely relied on case studies (Talih & Ajaltouni, 2015; Wong et al., 2015). Future research specifically focusing on

which substances are available and what side effects are associated with that type of nootropic, is required to reduce the harms associated with nootropic use. The current study therefore aims to provide a commentary of consumer experiences of nootropic use, with a focus on the mental health side effects for these consumers.

Current Study Aims

It appears that the nootropic market is accessible to consumers, but specific details such as nootropic type and availability are not yet clarified. Some of these substances being legal (e.g., Ginkgo Biloba and Piracetam) and some being illegal (e.g., modafinil and adrafinil; Australian Government Department of Health, 2017) to buy, further emphasises the need for an understanding of the nootropic drugs available to Australian consumers. More importantly, as both legal and illegal substances are available through the Internet but have not yet had safety testing (and are typically sold as being 'not for human consumption'), these substances may have unforeseen effects which need to be identified and further explored.

The current study aims to assess the existing nootropic market with an emphasis on substances available to Australians, through a 12-month pilot web monitoring system based on the methodologies of a previous Emerging Psychoactive Substances (EPS) monitoring framework (Bruno et al., 2013; Psychonaut Web Mapping Research Group, 2010). The 12-month monitoring will identify nootropics readily available to the Australian consumer. In addition to monitoring the nootropics and their respective online vendors, the current study also aims to provide a brief review of the 10 most commonly available nootropics from this monitoring period. Furthermore, qualitative information from popular online forums will be used to provide commentary on the potential side effects of nootropic use, with a focus on mental health effects of both one-

off and regular nootropic consumers. Overall, the study aims to provide a systematic approach to understanding nootropic substances and clinically relevant side effects.

Study 1

Method

Design

Study 1 utilised an Internet monitoring methodology previously used to monitor emerging psychoactive substance trends in Europe and Australia (Psychonaut Web Mapping Project, 2010; Bruno et al., 2013) to monitor nootropic substances. The monitoring system aimed to identify the number of vendors selling nootropic drugs, survival rates of these online vendors, and the types of nootropics available, within an Australian context. Monitoring was conducted on the surface web using popular search tools including Google, Yahoo, and Bing, as the aim was to mimic the search and access process that may be used by an individual consumer seeking to purchase these substances.

Procedure

Initial search process: Target identification. To identify frequently used Internet search terms for nootropics, common nootropic Internet forums were examined (e.g., www.reddit.com/r/nootropics; see Appendix A). Once common terms were identified (e.g., ‘smart drugs’; see Appendix B), they were analysed using Google Trends. Google Trends identifies how popular a search term has been for each country in the world on a relative scale of 1-100 during the last 12 months. The current study included Australian search terms that were identified to have a score of 30 or above. These included ‘smart drugs’, ‘nootropics Australia’, ‘modafinil’, ‘nootropic’, ‘noot’, ‘cognitive drugs’, ‘racetams’ and ‘cognitive enhancers’.

First month search process. The monitoring began in July 2017 and for the first month of monitoring, the eight identified search terms (i.e. smart drugs, nootropics Australia, modafinil, nootropic, noot, cognitive drugs, racetams and cognitive enhancers) were used. These terms were entered into the top three Australian search engines (i.e. google.com.au, yahoo.com, and bing.com; Statcounter Global Stats, 2016). Default search settings were used with no additional add-ons that could potentially block sites (e.g., ad blocker). The aim of this process was to replicate the experience of a consumer should they be conducting an Internet search for these products. Each search term was entered individually into each search engine to uncover nootropic vendors (i.e. websites that directly offered nootropics for sale). These searches for each term, on each search engine, were terminated after 100 search results discovered no new vendors.

When a vendor was identified to be selling nootropic drugs, it was checked to see if it would ship to Australian customers, by undergoing the procedure to purchase nootropics for sale and inputting an Australian shipping address. Only vendors that would ship to Australia were included in the monitoring. A listing of each vendor, and of the nootropic products that were available for sale to Australian based customers was made.

Second and subsequent month search process. Monitoring was conducted once a month, for 12 months, on the last seven days of each month. At each new monthly search phase, previously identified vendors were assessed directly to determine if they were still accessible. For each vendor, the products that they had available for sale to Australians were recorded. Each month, the initial list of search terms (i.e. smart drugs, nootropics Australia, modafinil, nootropic, noot, alpha brain, cognitive enhancer, and racetams) was entered into Google, Bing, and Yahoo search engines to identify

nootropic retailers. In addition, the names of the ten most commonly identified products identified for sale at vendors (e.g., Adrafinil) were added into the search list. In the first month these included Adrafinil, Noopeept, Phenibut, Aniracetam, Alpha GPC, Oxiracetam, L-theanine, Phenylpiracetam, Centrophoxine, and Pramiracetam. This list was cumulative with more terms being added each month. The drug name would remain in the search even if they were no longer in the top ten for that month. This process had been previously adopted in monitoring of novel psychoactive substances (Bruno et al., 2013; Van Buskirk, Roxburgh, Bruno, & Burns, 2013).

Results

The 12-month Internet monitoring revealed 52 unique web vendors selling nootropic substances available for purchase by Australian consumers. Of the vendors discovered, a total of nine vendors either closed, stopped taking new subscribers, or were inactive over the period of monitoring. An average of 0.8 (range 0-4) sites were gained per month, with an average of 1.6 (range 0-5) lost each month (see Figure 1). Vendors remained stable, with all vendors lasting at least seven months of monitoring. Interestingly, over the final six months, only 82.7% of vendors remained, with an average drop of 1.4% per month (range 0-5%; see Figure 2). Additionally, monitoring revealed a total of 342 nootropic substances available to the Australian consumer. Of the identified nootropics, 79.8% were specified compounds, with 48.7% of these specified compounds sold in blends (i.e. containing multiple substances). The remaining 20.2% were unspecified compounds, with 79.7% of these being sold in blends. An average of 8.3 (range 0-42) substances were added each month, with an average of 5.9 (range 0-17) lost each month (see Figure 3). After six months of monitoring, 96.0% of nootropic substances remained, with an average drop of 0.8% per month (range 0-2%; see Figure 4.)

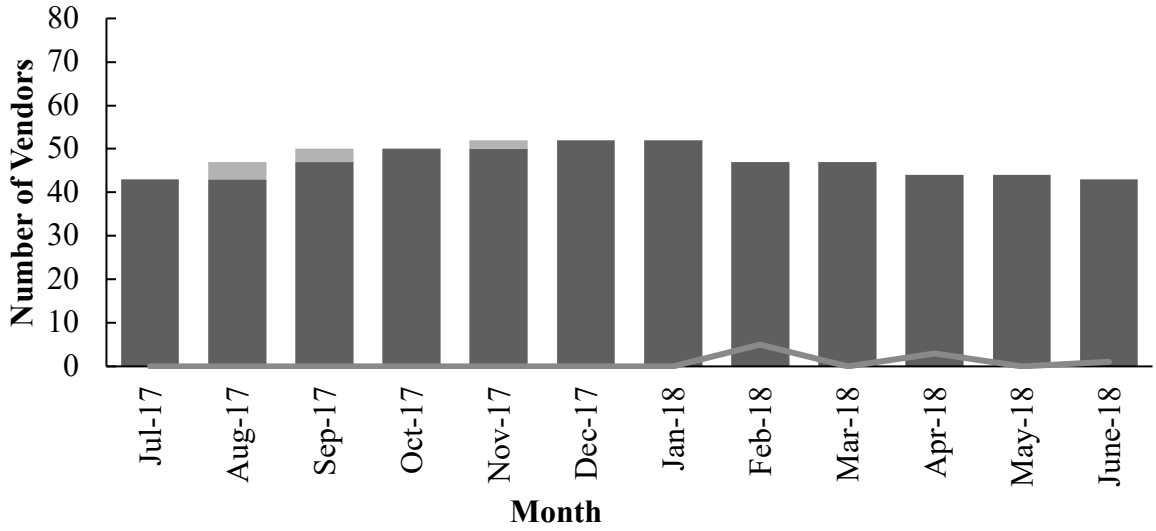


Figure 1. Vendors selling nootropics to Australians over the 12-month period. Light grey areas are new vendors identified each month, with the line indicating number of sites lost each month.

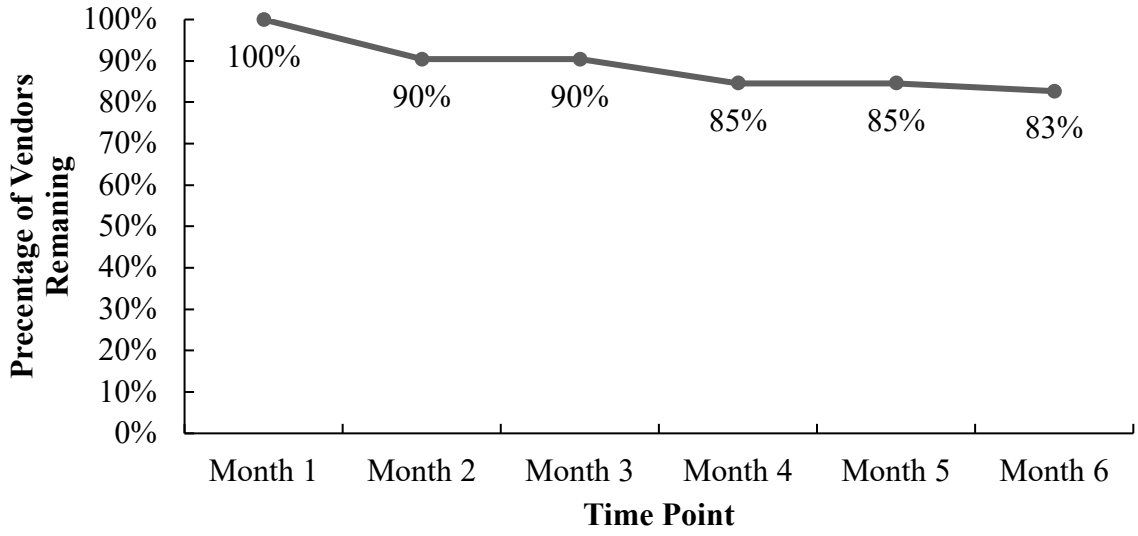


Figure 2. Percentage of vendors remaining during the final six-months of monitoring. Note: this includes only vendors first identified in the first 7 months of assessment

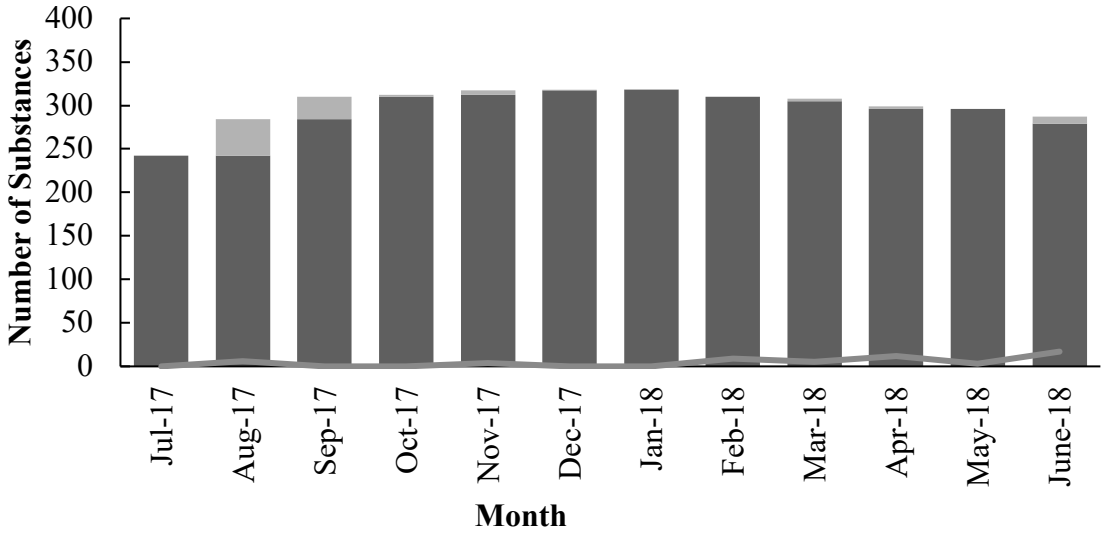


Figure 3. Nootropic substances available to Australians over the 12-month period. Light grey areas are new substances identified each month, with the line indicating number of substances lost each month.

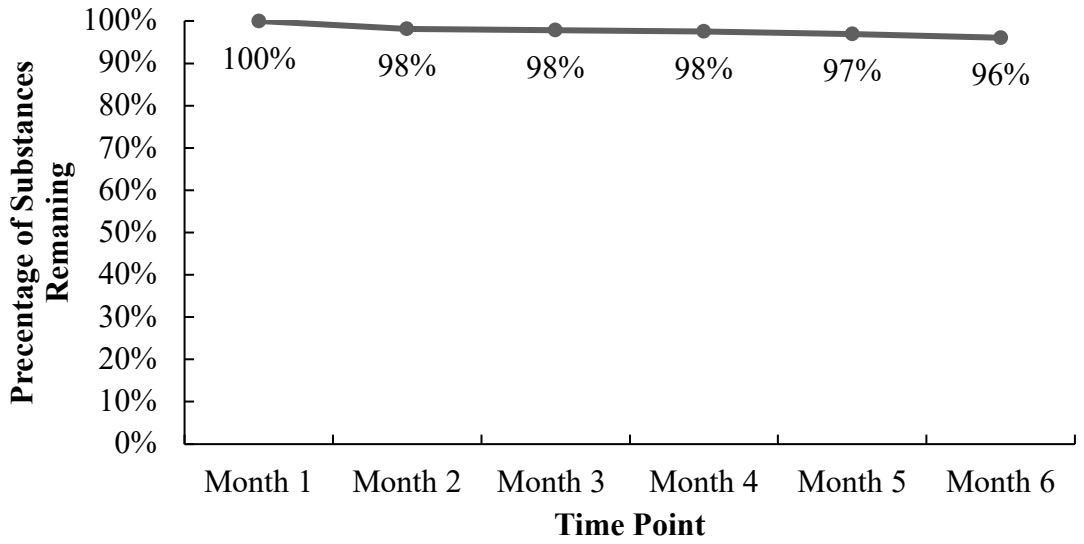


Figure 4. Percentage of substances remaining after a six-month period of monitoring. Note: this includes only vendors first identified in the first 7 months of assessment

A tabulated list of all nootropic substances identified are presented below (Box 1-3). The top ten most commonly available nootropic substances were Adrafinil, Alpha

GPC, Aniracetam, Centrophenoxine, L-theanine, Noopept, Oxiracetam, Phenibut, Phenylpiracetam, and Pramiracetam.

Box 1: All nootropics identified for sale to Australia as single products where content was specified to the consumer

5-HTP
ACAI
Acetyl-L-Carnitine
Adaptongen
Adrafinil
Agmatine Sulfate
ALCAR
Alpha GPC
Aniracetam
Ashwagandha
Bacopa Monniera
Baicalin
Barley Grass
BCAA
Berberine
BETA Alanine
Black Hoof Mushroom
Bromantane
Calcium D-Glucarate
CDP Choline
Centrophenoxine
Chaga Mushroom Extract
Choline Bitartrate
Cissus Quadrangularis
Citicoline
Cocoa Extract
Coenzye Q10
Coluracetam
Conjugated Linoleic Acid
Controlled Labs Gamer up
Cordyceps
Creatine
CRL 40,940
Curcumin
CX516
Cyclazodone
Cyracos Lemon Balm
Cytisine
DHA
DHM
Dihydroxyflavone
Dl-Phenylalanine
DM235
DMAE
DMHA
Dopamine
Emoxypine
EVP-6124
Exoxypine
Fasoracetam
Fenozolone
Forskolin
GABA
Galantamine
Gastrodin
Ginkgo Biloba
Ginseng
Goji Berries
GS15-4
Gynostemma
Hordenine
Huperzia Serrata
Huperzine A
Hydrafinil
Hydroxytyrosol
Hyperzine
Idebenone
IDRA-21
Inositol
Iodine
KSM-66
L-Arginine
L-Carnosine
L-dopa
Lecithin
Lion's Mane
L-Phenylalanine
L-theanine
L-tyrosine
MACA
Magnolia Bark Extract
Maitake
Melatonin
Memantine
Methyl Folate
Milk Thistle
Mitogen
Modafinil
Modalert
Modvigil
N-acetyl L-cystenine
N-acetyl L-tyrosine
N-acetylcysteine
NeuroMaster
Noopept
Octane
Omega-3 fish oil
Opti-Dhea
Oxiracetam
Palmitoylethanolamide
Phenibut
Phenylpiracetam
Phosphatidylserine
Picamilon
Piracetam
Policosanol
Polygala Tenuifolia
Poria
Pramiracetam
PRL-8-53
Pterostilbene
Purified Shilajit
Pyrroloquinoline
Red Relshi Mushroom
Reishi Mushroom
Resveratrol
Rhodiola Rosea 3
Royal Jelly
S17092
Sacred Lotus
SAMe
Serotonin
Sulbutiamine
Sunifiram
TeaCrine
Theacrine
Tianeptine
Tongkat
Toremifene Citrate
Tribulus
Trubrain
Unifiram
Uridine
Uridine Monophosphate
Valerian root
Vincamine
Vinpocetine
White Jelly Mushroom
Zembrin

Box 2: All nootropics identified for sale to Australia as multiple products combined as a bland where content was specified to the consumer

1-2 Go
7-keto DHEA
AAKG 2:1
Acetyl-L-Tyrosine
ActiGrape
ADK
Alaskrill Fish
Alpha Brain
Amino Focus
ANS Performance
Antarctic krill oil
Arginine
Alphaketogluterate
Ashwatrax
BaCognize
Biocreatine
Brain Antioxidai
Brain Elevate
Brain Smart Focus
Brain Smart Memory
Brain Smart Mood
Brain smart Ultra
BSN Neuro Fx
Bullet proof Ageing formula
Burner Combination
Caffeine/Nalt
Caffeine+ L-Theanine
Camellia Sinensis
Chocamine Plus
Choline & Inositol
Ciltep
CinnaTrax
Cleanse Liver Support
CoQsol-CF
Cratine Monohydrate
Creatine Ethyl Ester
Creatine Nitrate
Crossbiotics
D Aspartic Acid
D-Cycloserine
Diindolylmethane
DMAE L-Bitartrate
DopaTrax
D-Ribose
DTOX
EGCG
Evergreen Brain Function
Eye Armor
Ez Mega 3
FenuTrax
Flavonoids
Flow
Forbose
Fortilyte
Ginkgo Viloba
Glutathione
Grape seed extract
Green Tea Extract
HMB
Joints Capsules
KADO-3
KetoPrime
KetoShield
Konjac Root
Laxogenin
l-citrulline Dl-Malate
Lemon Balm
Liposomal Phenibut
Lithium
Lithium Orotate
Longvida
L-Phenylalanince
L-proline
Lutein& Zeaxanthin
Magnesium Aspartate
Magnesium L-Threonate
Magnesius L-threonate
Methyl B-12
Methylcobalamin
Methylene Blue
Mucuna
Mycomind
Myo-Inositol
N-Acetyl Semac Amidate
NADH
NA-R-ALA Stabilized R-Lipoic
Neuro Fx
Neuro Vita
Neurochill
Neuroprime
Nexus
Niacinamide
Noocube
Optimal Sleep
OptiVasc
Panax Ginseng
Pantethine
PEA-P HCI
Perluxan
Phenibut FFA
Phenibut/Insositol
Polyphenomenal
PPAP HCI
PQQ
Probiotic complex
Proviotic
Pump Fx
Pyridoxine HCL
R Alpha Lipoic
Racetam
R-ALA Cyclodextrin
Raloxifene
R-alpha-Lipoic-acid
Rasberry Ketone
RGPU-95
Rhodiola crenulata
Schizandrol A
Semax
SR-9009
Sucralose
Sunhorse Energy NanoMojo Liposomal Adaptogenic
Super B12
Super Rhodiola
Taurine
TestoTrax
Thozalinone
Turkey Tail
Ultra Caffeine
Unfair Advantage
VibraJoint
Vinpocetine
Vitalify
Wellness Formula
Zinc with copper
ZMA

Box 3: All nootropics identified for sale to Australia as single or multiple products combined

as a bland where content was not specified to the consumer

Adaptrax
Ageless
AMP'D
Artvigil
BCAA 2-1-1
Brain Minits
Brain speed
Brain stack
Cortex
DMAA
DNA Pharma
Doze
Electrolyte
Epicor
Fladrafinil
focus up
Focus3d
GTS-21 HCI
HemoLift
Immuni Prime
IQUZIL
Kimera
Kudingcha Tea
Limitless NZT-48+Restoramones
Magtech
Memory Complex
Mind Lab Pro
MODafinil
Modafy
Mood and Memory
Mycoboost
N03X
Nefiracetam
Neourodrive
Nootroo
Nootropics Brain support
Nootropix
Noowave POWR
NooWave SWELL
NSI-189
NutraDIM
NutraRez
Pamella
Peak Chocolate
Pomella
Pregnenolone
Prevagen
Pre-Workout Nootropic
Pyritinol HCL
Rave
Rise
Senegenin
Sensoril
Sleep Mode
Sprint
Study Juice
switch
Synapsa
Thermal Switch
Think-Rite
Total Focus
Tranquilora
Triacetyluridine
True Calm
Ultracholine
Unwind
Waklert
Yawn
Zen mode

Preliminary Discussion

The current study assessed the existing nootropic market available to Australian consumers over a 12-month period, using similar methodologies to other monitoring studies of substances operating in legally grey areas such as novel psychoactive substances (Bruno et al., 2013). The monitoring revealed a substantial number of vendors that Australian consumers could access and order nootropic substances from. These vendors had a large variety of nootropics available, all advertising cognitive enhancements. In line with previous research, the monitoring revealed several different types of nootropics were available, such as prescription pharmaceuticals (e.g., modafinil), synthetic compounds (e.g., Oxiracetam, Noopept, and Adrafinil), and naturally occurring substances (e.g., Bacopa Monnieri, Ginkgo Biloba, and Lion's Mane). Substances were commonly sold in the form of tablets, powders, and liquids, as both specified and unspecified compounds and blends. The nootropic market was stable across the 12 months of monitoring and the current study has provided an accurate picture of the existing nootropics available to the Australian consumer.

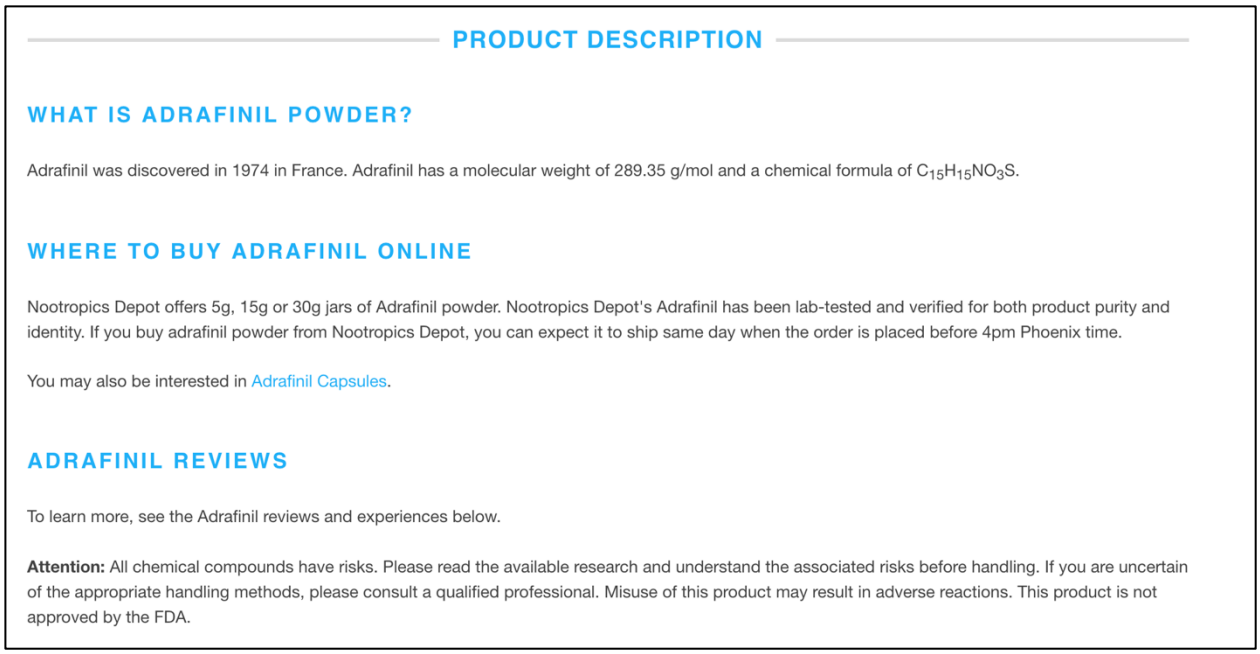
Interestingly, stores would often advertise cognitive benefits of the nootropics in a variety of ways. Some vendors would use professional reviews (purported to be) from individuals working in fields related to cognitive ability (e.g., psychologists, neurologists, and doctors: see Table 3). These forms of advertising appeared to use the credibility of professionals to instil trust in the nootropic products, similar to medications advertised online (Hoffman & Wilkes, 1999). Other vendors provided links to research for each available nootropic, which highlighted that particular nootropics researched benefits. Consistent with the current literature, these were often animal studies (Ahmad et al., 2017). Additionally, these studies were often difficult to interpret due to their complex scientific language. Most vendors provided consumer reviews of

specific products or links to forums such as r/Nootopics. The majority of vendors did not provide any information on adverse side effects associated with mental health. Specifically, vendors would often list positive benefits in the nootropic product description with limited to no information of perceived side effects (see Figure 5). It is conceivable that it would be difficult for consumers to filter through the provided information to identify and be fully informed regarding the potential cognitive benefits, research identifying benefits, and potential side effects associated with each nootropic available. Additionally, consumers may be susceptible to confirmation bias focusing on information presenting potential benefits, rather than negative side effects. These factors make it difficult for consumers to be informed when purchasing nootropics online. The Therapeutic Goods and Administration Board requires a comprehensive description of pharmaceuticals (see Figure 6) to ensure transparency for consumers, something currently absent from nootropic vendors. With the information presented to consumers not detailing sufficient information to inform the consumer, individuals will have difficulty identifying information that is important to prevent risk (e.g., recommended dosage, what side effects are possible and when to become concerned when using the nootropic they have purchased online).

Table 3

Examples of Endorsement of Nootropic Vendors

Nootropic Name	Examples
MindLabPro	 **Dr. Paul Nussbaum** Clinical Neuropsychologist
Noocube	 *"I started feeling the effects of NooCube from the very first day, there's nothing else quite like it.* MARK B Sports Psychologist
Axonlabs	 **Robert Ness** Statistician - Systems Biology *"To help with dissertation writing, I've tried smart drugs on top of good diet, exercise, and plenty of rest. I've tried Ritalin, Adderall, Provigil, nicotine, *lots* of caffeine, and now NEXUS. NEXUS wins."*  **Laura Styler** Diagnosed in 2011 with MTHFR *"I have chronic toxin build-up, and I'm constantly looking for ways to help my detox pathways work better. NEXUS and MITOGEN have been amazing for both my mental and physical stamina."*  **Ben Pomeroy** Digital Media Director *"NEXUS is great. I felt clear-headed, motivated, not at all wired, and went on like that for hours. In my work, the ability to drop into 'the Zone' like that is gold."*



PRODUCT DESCRIPTION

WHAT IS ADRAFINIL POWDER?

Adrafinil was discovered in 1974 in France. Adrafinil has a molecular weight of 289.35 g/mol and a chemical formula of $C_{15}H_{15}NO_3S$.

WHERE TO BUY ADRAFINIL ONLINE

Nootropics Depot offers 5g, 15g or 30g jars of Adrafinil powder. Nootropics Depot's Adrafinil has been lab-tested and verified for both product purity and identity. If you buy adrafinil powder from Nootropics Depot, you can expect it to ship same day when the order is placed before 4pm Phoenix time.

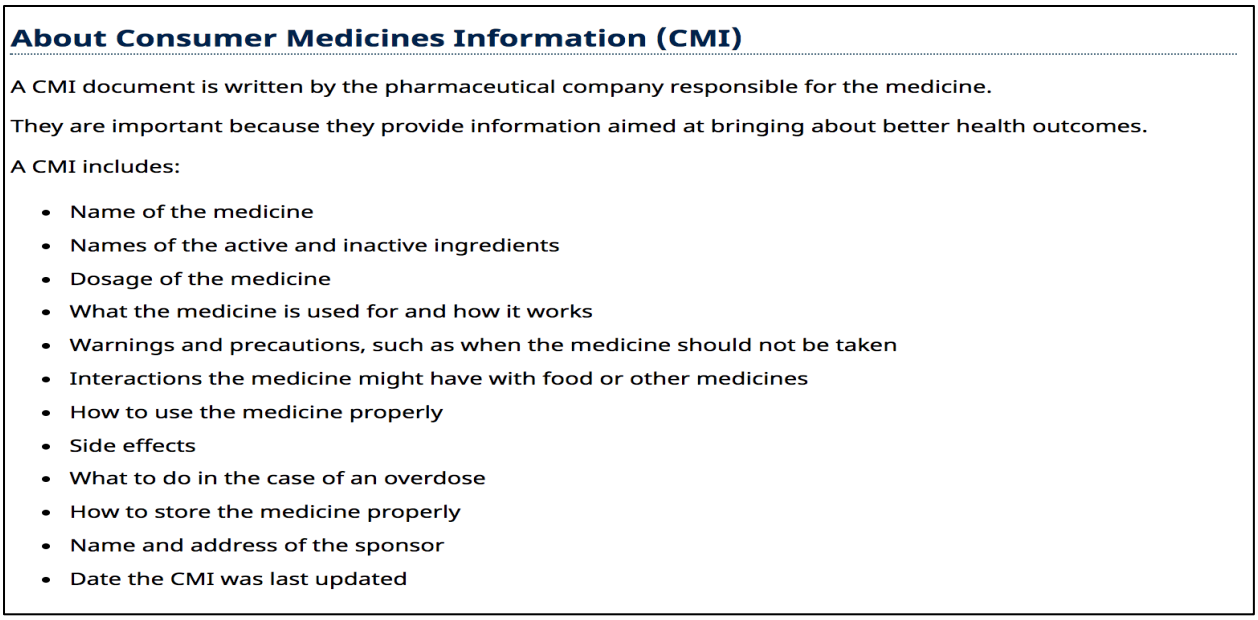
You may also be interested in Adrafinil Capsules.

ADRAFINIL REVIEWS

To learn more, see the Adrafinil reviews and experiences below.

Attention: All chemical compounds have risks. Please read the available research and understand the associated risks before handling. If you are uncertain of the appropriate handling methods, please consult a qualified professional. Misuse of this product may result in adverse reactions. This product is not approved by the FDA.

Figure 5. Example of product description provided (Nootropicsdepot, October 3, 2018). Note that the parent drug, modafinil, is prescribed in doses of 200mg, and the more active adrafinil is sold in quantities of 5-30g.



About Consumer Medicines Information (CMI)

A CMI document is written by the pharmaceutical company responsible for the medicine.

They are important because they provide information aimed at bringing about better health outcomes.

A CMI includes:

- Name of the medicine
- Names of the active and inactive ingredients
- Dosage of the medicine
- What the medicine is used for and how it works
- Warnings and precautions, such as when the medicine should not be taken
- Interactions the medicine might have with food or other medicines
- How to use the medicine properly
- Side effects
- What to do in the case of an overdose
- How to store the medicine properly
- Name and address of the sponsor
- Date the CMI was last updated

*Figure 6.*Consumer medicines information guidelines (Australian Government Department of Health, October 3, 2018)

In line with previous Australian research, racetam (e.g., Piracetam and Aniracetam) based nootropics were readily available to the consumer across most vendors, with Aniracetam, Oxiracetam, Phenylpiracetam, and Pramiracetam being in the

top ten most commonly available nootropics presented in Table 4 (Nelson & Lenton, 2017). Conversely, forms of modafinil (e.g., Provigil, Modvigil, Modalert, and Alertec) were not frequently discovered during the monitoring, despite previous research suggesting modafinil is a popular nootropic (Nelson & Lenton, 2017). This may be further explained by modafinil being a Schedule 4 (i.e. a medication that requires a prescription from a doctor) substance in Australia (Australian Government Department of Health, 2017), and is therefore less likely to be sold illegally from an online vendor. Further information supporting this trend, comes from previous research establishing that Australian consumers purchased their modafinil from a dealer or friend (Nelson & Lenton, 2017).

Table 4

Twenty Common Nootropics identified from Vendors Each Month

Month	1	2	3	4	5	6	7	8	9	10	11	12
Adrafinil	11	17	17	17	17	17	17	14	14	13	13	13
Alpha GPC	10	15	18	18	18	18	18	15	15	13	13	14
Aniracetam	10	12	14	14	14	14	14	11	11	10	10	12
Noopept	10	13	15	15	16	16	16	13	13	12	11	12
Oxiracetam	10	13	15	15	15	15	16	13	13	12	12	13
Phenibut	10	12	13	13	13	13	13	10	10	10	10	12
Centrophenoxine	8	11	11	11	11	11	11	10	10	10	10	10
L-theanine	8	12	17	20	17	17	17	15	15	14	14	16
Phenylpiracetam	8	11	13	12	12	12	12	9	9	9	10	10
Pramiracetam	8	12	12	13	14	13	13	11	11	10	9	12
Number of vendors	43	47	50	50	52	52	52	47	47	44	44	43

Month	1	2	3	4	5	6	7	8	9	10	11	12
5-HTP	7	9	9	9	10	10	10	8	8	7	6	5
PRL-8-53	7	9	9	9	9	9	9	6	6	5	5	5
Sunifiram	6	9	10	10	10	10	9	6	6	5	5	5
Tianeptine	6	9	10	10	10	10	9	7	7	7	7	7
Acetyl-L-Carnitine	5	6	7	7	6	6	6	6	6	6	6	6
Bacopa Monniera	5	8	9	9	9	9	9	9	9	9	9	8
Choline Bitartrate	5	8	9	9	9	9	9	8	8	8	8	7
Citicoline	5	5	6	6	6	6	6	5	5	5	5	5
Coluracetam	5	8	9	9	9	9	9	7	7	6	6	7
Piracetam	5	5	6	6	6	6	6	5	6	6	6	6
Number of vendors	43	47	50	50	52	52	52	47	47	44	44	43

Although modafinil was not identified as a top ten most common nootropic, Adrafinil, a nootropic that metabolises as modafinil, was. Adrafinil is also a Schedule 4 substance (Australian Government Department of Health, 2017), however it was available to be ordered and shipped to Australia from a variety of vendors. Adrafinil still being sold to Australian consumers regardless of its restrictions, may be a result of consumers taking the risk and ordering a less known nootropic and hoping that it will be processed through Australian customs. Importantly, many of the vendors indicated that they held no responsibility for purchases that were taken by the respective country customs department. The current study did not order any nootropics from vendors to trial if they would get past Australian customs. Adrafinil was the only nootropic in the top ten most common nootropics that is currently a Schedule 4 restricted substance and

was included in case it was available to order into Australia without being detected. Of note, crypto currency (e.g., Bitcoin, Skirll, light coin, Bitcoin Cash, and Ethereum), an online currency that offers anonymity, was accepted by 20.5% of vendors, which allows the purchasing of these restricted substances anonymously (Phillip, Chan, & Peiris, 2018). The method of using anonymous currency is extensively utilised in the purchasing of controlled substances (e.g., ecstasy, opioids, and psychedelics), due to the transaction being difficult to link back to the consumer (Barratt, 2012).

Nootropics that through previous research have been found to have psychological side effects, were also discovered by the monitoring. Specifically, Phenibut was one of the top ten most common nootropics discovered and has been identified as a substance with concerning adverse side effects (McNeilage, 2018; Wong et al., 2015). Additionally, racetams such as Aniracetam, Oxiracetam, Phenylpiracetam, and Pramiracetam have been noted to result in psychopathological symptoms (e.g., anxiety; Nelson & Lenton, 2017). Alarmingly, some vendors provided measuring equipment (e.g., scales) and powder nootropics, encouraging consumers to make their own blends. This is of concern as nootropics research is in its infancy and there is a substantial gap in research focusing on the side effects of nootropics and potential interactions of other substances the consumer is taking. Parallels between nootropics and performance enhancing substances (e.g., anabolic androgenic steroids and growth hormones) commonly used in body building can be drawn, due to consumers often using substances unsupervised and without input from physicians (El-Reshaid, El-Reshaid, Al-Bader, Ramadan, & Madda, 2018). The body building substance literature has identified concerning risks such as kidney disease and heart failure (El-Reshaid et al., 2018; White, Brennan, Ren, Shi, & Thakrar, 2018). Nootropics research requires a

similar focus on risk, as comparable unsupervised consumers that are encouraged to create homemade blends, require monitoring and accurate information regarding potential side effects to reduce risk (Ahmad et al., 2017; Talih & Ajaltouni, 2015; Wong et al., 2015).

Although the larger nootropic market appears to be stable compared to other emergent substances (Bruno et al., 2013), it is important for clinicians to be aware of the potential side effects of nootropics (Talih & Ajaltouni, 2015). As a variety of nootropics are available, clinicians require an understanding of available drugs and their impacts on human behaviour to correctly formulate a client's presentation. Mental health workers (e.g., psychologists) would benefit from more research and detailed information regarding the potential mental health side effects of these substances. To initiate increased awareness of side effects that are being experienced by consumers, Study 2 of this paper will explore consumer reviews for the top ten most common nootropics (as found in Study 1).

As previously mentioned, a limitation of the current study is that no nootropic substances were ordered from vendors. Because of this, the study is limited in unquestionably identifying the specific nootropics that are available for the Australian consumer. For example, controlled substances such as modafinil and Adrafinil could be taken by Australian Customs and not delivered to the consumer. Additionally, consumer reviews reported vendors are claiming to sell certain nootropics, however after receiving them found they were not the nootropics they were advertised as being. Specifically, WEDINOS a website aimed at harm reduction by testing substances purchased online, found certain nootropics were not the substance the consumer had ordered (Wedinos, 25 September, 2018). Table 5 displays examples of times consumers had ordered nootropic

substances (e.g., Modafinil) and when tested the substance was another (e.g., cocaine). Table 5 also presents examples of the times a consumer had reported negative side effects (e.g., hallucinations, nausea, panic attacks, agitation, and insomnia) as a result of taking the unanticipated substance. As the current study did not order any nootropics, it was not possible to verify whether the advertised nootropics were actually provided. Furthermore, the study was unable to note how widespread or likely it would be for a consumer to receive an unanticipated substance. An additional limitation is the broad definition of nootropic substances and the difficulty in grouping all the nootropics found. The current literature suggests that nootropics is a broad term that needs further defining, however at this stage no concrete classifications of these substances exists (Angeles, Ples, & Vitor, 2018). Future research should focus on defining nootropics further and testing nootropics for purity to better understand the market.

Table 5
Example of Nootropic Sample Reports that Revealed Unanticipated Substances (Wedinos, 25 September, 2018)

Intended substance	Year tested	Actual substance	Reported side effects
Adrafinil	2015	Unable to identify	Increased energy.
Armodafinil	2017j	Unable to identify	Visual hallucinations, breathlessness, chest pain, nausea, panic attacks, and loss of consciousness.
Modafinil	2014	Cocaine + Benzocaine	N/A
Modafinil	2015	Caffeine + Vitamin B3	N/A
Modafinil	2017	Cocaine + Levamisole	N/A
Phenibut	2018	Caffeine + Amphetamine	Increased energy, hallucinations, panic

	attacks, nausea, agitation, and insomnia.

Retrieved from http://www.wedinos.org/

Study 2

Study 2 aimed to explore consumer reviews for the top ten most common nootropics identified in Study 1 (i.e. Adrafinil, Alpha GPC, Aniracetam, Centrophenoxine, L-theanine, Noopept, Oxiracetam, Phenibut, Phenylpiracetam, and Pramiracetam), to initiate increased awareness of the side effects being experienced by consumers.

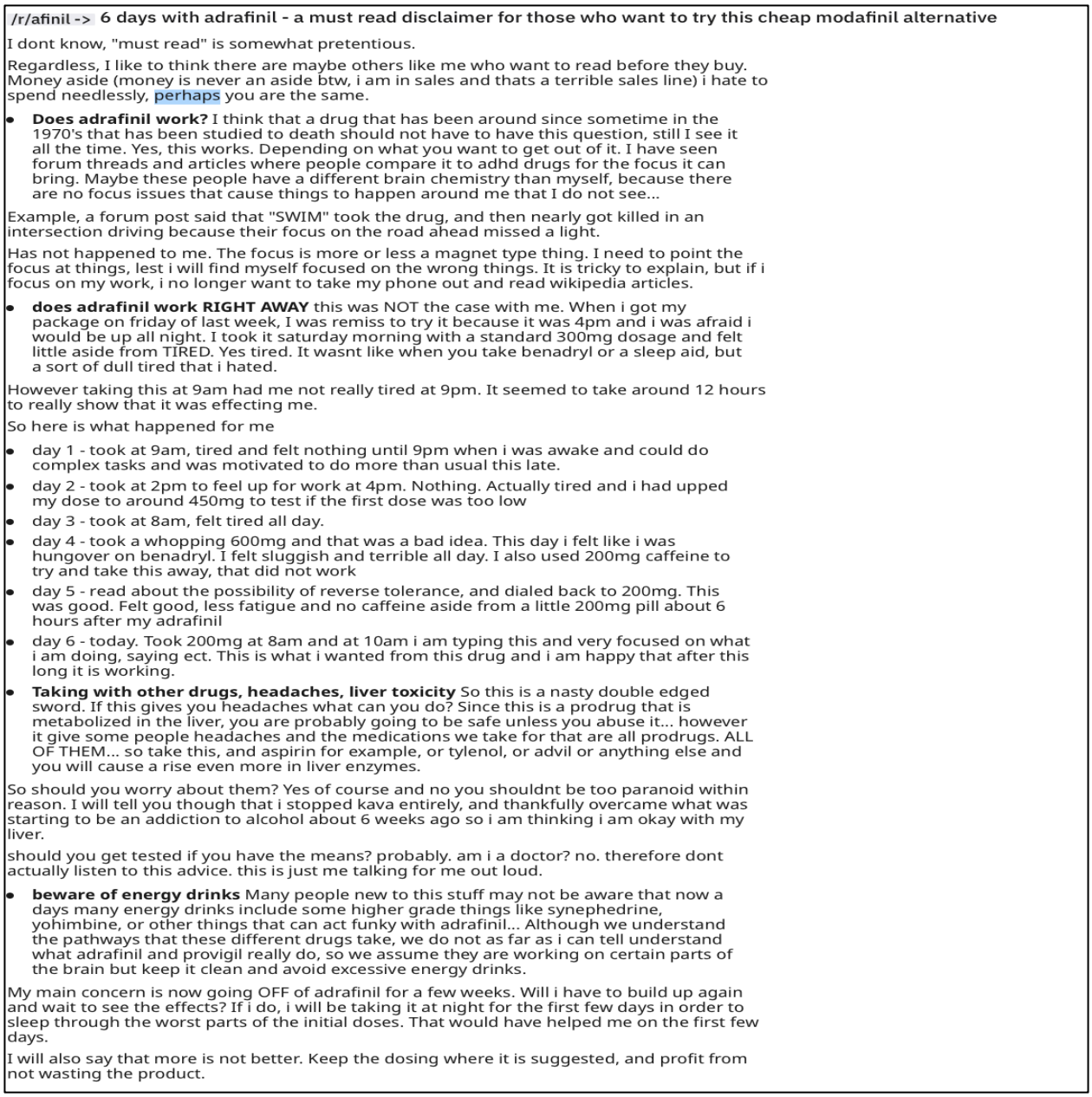
Method

Participants

Participants were consumers of any of the top ten nootropic drugs identified in Study 1, who had reported their experiences on open Internet forums.

Apparatus

Key Internet forums were examined in order to gather consumer reports of use of these substances (r/nootropics.com, Drugs-Forum.com, and Whirlpool.com). Due to the relatively scientific manner that consumers reported and described their nootropic experiences, these sites were identified as providing an adequate representation of the general consumer. Consumer reports ranged in the amount detail provided and the approach to individual's reports (see Figures 7 and 8). Consent was implied due to consumers posting their experiences in public forums (Golder, Ahmed, Norman, & Booth, 2017; Roberts, 2015). All forum threads reviewed were accessible to the public, with consumers aware of this accessibility.



/r/afinil -> **6 days with adrafinil - a must read disclaimer for those who want to try this cheap modafinil alternative**

I dont know, "must read" is somewhat pretentious.

Regardless, I like to think there are maybe others like me who want to read before they buy. Money aside (money is never an aside btw, i am in sales and thats a terrible sales line) i hate to spend needlessly, perhaps you are the same.

- **Does adrafinil work?** I think that a drug that has been around since sometime in the 1970's that has been studied to death should not have to have this question, still I see it all the time. Yes, this works. Depending on what you want to get out of it. I have seen forum threads and articles where people compare it to adhd drugs for the focus it can bring. Maybe these people have a different brain chemistry than myself, because there are no focus issues that cause things to happen around me that I do not see...

Example, a forum post said that "SWIM" took the drug, and then nearly got killed in an intersection driving because their focus on the road ahead missed a light.

Has not happened to me. The focus is more or less a magnet type thing. I need to point the focus at things, lest i will find myself focused on the wrong things. It is tricky to explain, but if i focus on my work, i no longer want to take my phone out and read wikipedia articles.

- **does adrafinil work RIGHT AWAY** this was NOT the case with me. When i got my package on friday of last week, I was remiss to try it because it was 4pm and i was afraid i would be up all night. I took it saturday morning with a standard 300mg dosage and felt little aside from TIRED. Yes tired. It wasnt like when you take benadryl or a sleep aid, but a sort of dull tired that i hated.

However taking this at 9am had me not really tired at 9pm. It seemed to take around 12 hours to really show that it was effecting me.

So here is what happened for me

- day 1 - took at 9am, tired and felt nothing until 9pm when i was awake and could do complex tasks and was motivated to do more than usual this late.
- day 2 - took at 2pm to feel up for work at 4pm. Nothing. Actually tired and i had upped my dose to around 450mg to test if the first dose was too low
- day 3 - took at 8am, felt tired all day.
- day 4 - took a whopping 600mg and that was a bad idea. This day i felt like i was hungover on benadryl. I felt sluggish and terrible all day. I also used 200mg caffeine to try and take this away, that did not work
- day 5 - read about the possibility of reverse tolerance, and dialed back to 200mg. This was good. Felt good, less fatigue and no caffeine aside from a little 200mg pill about 6 hours after my adrafinil
- day 6 - today. Took 200mg at 8am and at 10am i am typing this and very focused on what i am doing, saying ect. This is what i wanted from this drug and i am happy that after this long it is working.
- **Taking with other drugs, headaches, liver toxicity** So this is a nasty double edged sword. If this gives you headaches what can you do? Since this is a prodrug that is metabolized in the liver, you are probably going to be safe unless you abuse it... however it give some people headaches and the medications we take for that are all prodrugs. ALL OF THEM... so take this, and aspirin for example, or tylenol, or advil or anything else and you will cause a rise even more in liver enzymes.

So should you worry about them? Yes of course and no you shouldnt be too paranoid within reason. I will tell you though that i stopped kava entirely, and thankfully overcame what was starting to be an addiction to alcohol about 6 weeks ago so i am thinking i am okay with my liver.

should you get tested if you have the means? probably. am i a doctor? no. therefore dont actually listen to this advice. this is just me talking for me out loud.

- **beware of energy drinks** Many people new to this stuff may not be aware that now a days many energy drinks include some higher grade things like synephedrine, yohimbine, or other things that can act funky with adrafinil... Although we understand the pathways that these different drugs take, we do not as far as i can tell understand what adrafinil and provigil really do, so we assume they are working on certain parts of the brain but keep it clean and avoid excessive energy drinks.

My main concern is now going OFF of adrafinil for a few weeks. Will i have to build up again and wait to see the effects? If i do, i will be taking it at night for the first few days in order to sleep through the worst parts of the initial doses. That would have helped me on the first few days.

I will also say that more is not better. Keep the dosing where it is suggested, and profit from not wasting the product.

Figure 7. Example of a detailed consumer report.

I take 200 mg of L-theanine in the morning for one week. I noticed these side effects:

1. sleepwalking
2. headache
3. lower concentration
4. nausea
5. weight loss

So today I went to only 100 mg in the morning. I will see if this will change something.

I also take venlafaxine, 25 mg in the morning and 25 mg in the evening and olanzapine, 2.5 mg in the evening.

I don't know why is l-theanine over the counter drug, since it has such strong side effects :(.

Update: The side effects started just after I begun taking L-theanine. I was taking venlafaxine and olanzapine previously for years and there were no side effects mentioned here.

Figure 8. Example of a non-detailed consumer report.

Procedure

The top ten nootropic substances most commonly available to the Australian consumer were identified through the 12-month monitoring pilot study. The second study used these ten nootropics and public forums to gather consumer reports and experiences specifically related to these nootropics.

Firstly, each nootropic was examined separately via the three forums' search tool to reveal available consumer reports. The aim of investigating these consumer reports was to identify potential risks, with a focus on adverse mental health side effects for each nootropic. Any consumer report that made reference to one or more of the ten nootropics, and one or more negative side effects was included. Consumer reports posted within the last 10 years were included in the study. Secondly, each nootropic was entered into MEDLINE (United States National Library of Medicine, 23 August, 2018), a database constructed by the United States National Library of Medicine, to locate any available case studies or literature that involved each respective nootropic. Furthermore, brief literature searches were conducted to construct a basic understating of each nootropic and its intended action. MEDLINE searches additionally provided clarity on the chemical structure, pharmacodynamics/pharmacology and chemical analogy (i.e.

similar substituted medications). Figure 9 provides visual representation of the process followed to create the narrative review.

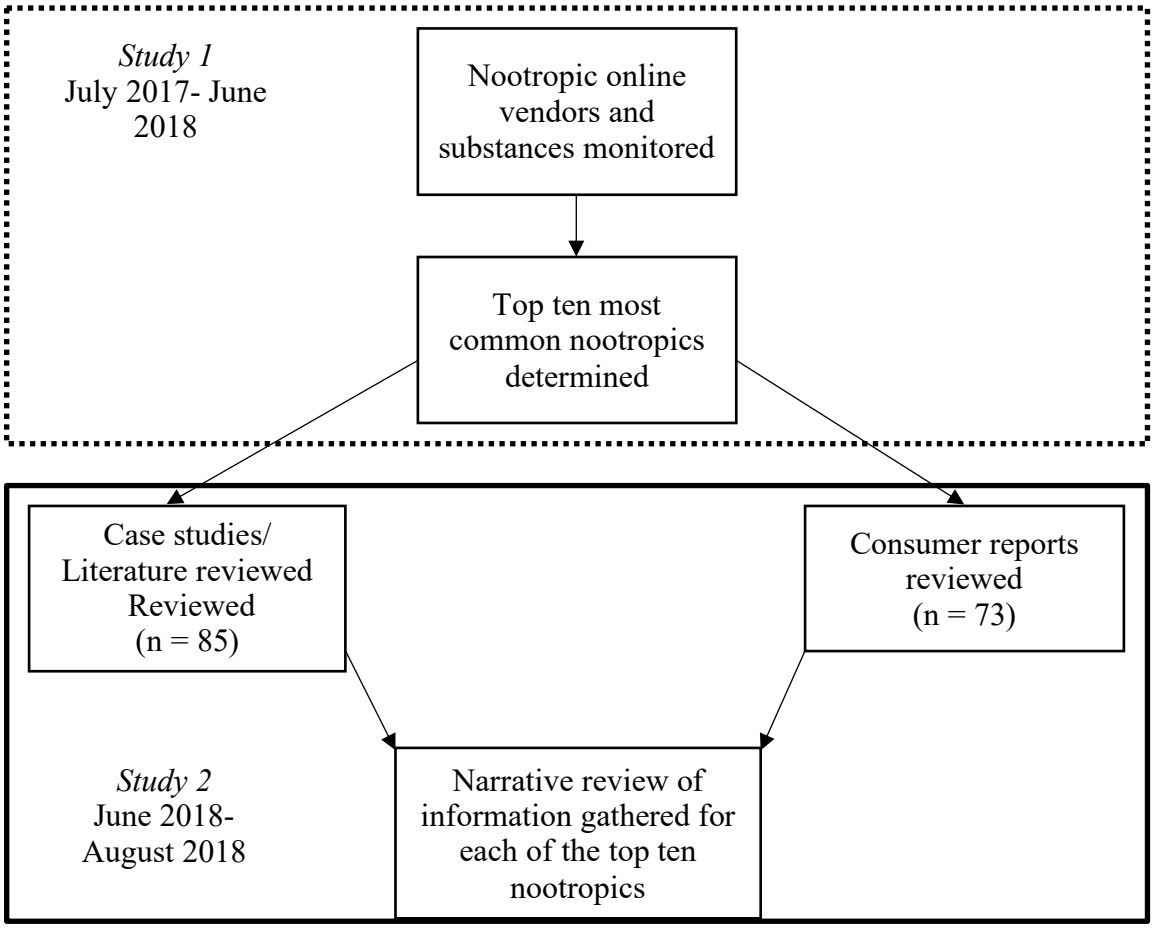
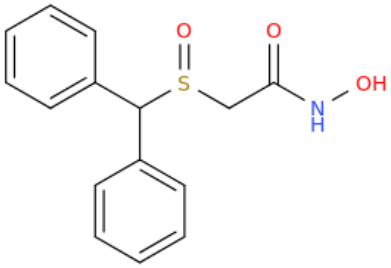


Figure 9. *Narrative review flow chart*

A narrative of the obtained details for each nootropic was organized and summarised to identify the chemical structure and potential mental health side effects. Overall, 73 consumer reports were reviewed (i.e. 16 for Adrafinil, eight for Alpha GPC, seven for Aniracetam, five for Centrophenoxine, 16 for L-theanine, three for Noopept, five for Oxiracetam, nine for Phenibut, four for Phenylpiracetam, and seven for Pramiracetam), and 85 case studies and literature reviewed.

Results

Adrafinil



a) **International Union of Pure and Applied Chemistry name (IUPAC name):** (±)-2-Benzhydrylsulfinylethanehydroxamic acid.

b) **Description:** Adrafinil is a nootropic substance first discovered in 1974 by L. Lafon Ltd and was used for patients who were narcoleptics (Billiard & Broughton, in press). It was marketed in France in 1985 under the name Olmifon with an indication of attention and motor impairment in the elderly, and was withdrawn from market in 2011 as there was insufficient evidence to conclude a positive risk/benefit ratio from existing safety and efficacy data (French National Agency for Medicines and Health Products Safety, 25 July, 2018). Once Adrafinil is consumed, it metabolises and becomes modafinil. Adrafinil has similar reported benefits (e.g., wakefulness and focus) as modafinil, however has been noted by consumers to be less effective. Animal studies have revealed that Adrafinil increases EEG (electroencephalograph) activity in the prefrontal cortex and has potential as a novel behavioural stimulant (i.e. increased locomotion and alertness), with the underlying mechanism of action still being unclear (Siwak, Callahan, & Milgram 2000; Siwak, Gruet, Woehrlé, Muggenburg, Murphey, & Milgram, 2000; Siwak, Tapp, & Milgram 2003). Conversely, Siwak et al. (2003) reported a significant decrease in working memory of beagles when given

Adrafinil, with these authors suggesting that this effect may have arisen from an observed increase in noradrenergic transmission in the prefrontal cortex.

c) **Chemical analogy:** As previously stated, Adrafinil metabolises to modafinil, a well-known prescription nootropic. Similar to Adrafinil, the exact mechanism of action of modafinil is unknown (Billiard & Broughton, in press). Clinical trials have indicated efficacy of modafinil in the treatment of narcolepsy and excessive sleepiness due to obstructive sleep apnoea and shift work. The Consumer Medicine Information (CMI; Consumer Medicine Information, 2017) product information sheet for modafinil includes a number of adverse side effects including increased aggressive behaviour, increased suicidal ideation, worsening of psychotic/manic symptoms, increased depressive symptoms, and increased anxiety.

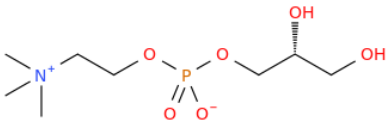
d) **Case studies:** Thobois, Xie, Mollion, Benatru, and Broussolle (2004) examined the case of a 75-year-old male who developed repetitive involuntary facial movements (i.e. orofacial dyskinesia) as a result of Adrafinil, prescribed for excessive daytime sleepiness. These symptoms persisted for four months after the Adrafinil was ceased. Thobois et al. (2004) noted that this was the first reported case of Adrafinil induced orofacial abnormal movements, with the reason for this interaction remaining unclear.

e) **Reported psychological side effects:** There were 16 consumer experience reports identified for Adrafinil. Four consumers identified in the current study, reported feelings of increased anxiety. Additionally, anti-social traits were indicated by a consumer who noted feeling "*cold blooded*" and "*cold hearted*"

(Reddit Consumer). Another consumer indicated feeling hyperactive and obsessive at times.

f) **Other reported side effects:** Consumers in the current study reported low energy, sleeping difficulties, tiredness, physical discomfort, skin irritation, dizziness, nightmares, and strained vision.

Alpha GPC



a) **IUPAC name:** [(2*R*)-2,3-Dihydroxypropyl] 2-trimethylazaniumylethyl phosphate.

b) **Description:** L-Alpha glycerylphosphorylcholine (Alpha GPC) is a nootropic that aims to enhance memory and learning by increasing the release of acetylcholine in the brain (Parker, Byars, Purpura, & Jäger, 2015). Alpha GPC has shown potential in reducing the symptoms of dementia (e.g., memory loss and alertness; Muratorio et al., 1992; Perri, Coppola, Ambrosio, Grasso, Puca, & Rizzo, 1991; Scapicchio, 2013). Cruse (2018) examined the cognitive impacts in a small sample (n = 27) of young adults, with findings suggesting that individuals who were given Alpha GPC performed significantly better in terms of reaction time on computer-based assessment tools. Cruse (2018) noted an absence of literature regarding the cognitive benefits of Alpha GPC. In addition to the cognitive benefits, Alpha GPC has also been assessed for its possible physical benefits (Marcus, Soileau, Judge, & Bellar, 2017). The US Food and Drug Administration have recognised that doses to a maximum of 196.2 mg/day meets the 'Generally Recognised as Safe' criteria (Heimbach, 2012).

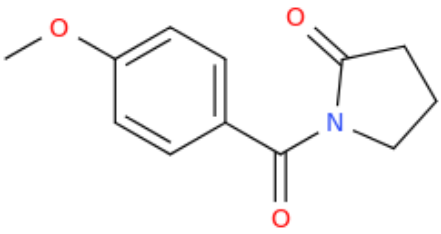
c) **Chemical analogy:** Choline or acetylcholine (Parnetti, Mignini, Tomassoni, Traini & Amenta, 2007). Alpha GPC is a precursor to choline and acetylcholine (on ingestion it is converted to phosphorylcholine and then to choline which is then available for biological synthesis of acetylcholine; Parnetti et al., 2007).

d) **Case studies:** To the authors knowledge no case studies have been published on Alpha GPC.

e) **Reported psychological side effects:** There were eight consumer experience reports identified for Alpha GPC. Consumers reported anxiety after using Alpha GPC. One consumer stated "*I couldn't believe it was anxiety at first either but it is. It was hard for me to believe it was anxiety at first too because I've always associated anxiety with how I feel in my mind, but for some reason in these situations it's just that we feel the physical effects of anxiety more than usual i.e. shortness of breath"* (Reddit Consumer). In addition to anxiety, consumers reported low mood (e.g., *"I got SO depressed after taking it. Darkest I've ever been"*; Reddit Consumer). Other consumers reported increased irritability, but not low mood (e.g., "It can make me irritable, but not depressed usually"; Reddit Consumer).

f) **Other reported side effects:** Consumers reported weight gain, low blood pressure, poor sleep, and mild headaches. Given that Alpha GPC increases choline levels in the central nervous system, this will interact with other acetylcholine enhancing medications such as those used in dementia; and will interact with acetylcholine inhibitors such as anticholinergics.

Aniracetam



a) **IUPAC name:** 1-[(4-Methoxybenzoyl)]-2-pyrrolidinone.

b) **Description:** Aniracetam is also known as N-anisoyl-2-pyrrolidinone and is a positive allosteric modulator at AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) glutamate receptors (Reynolds et al., 2017; Lee & Benfield, 1994). Given that glutamate is a general excitatory neurotransmitter, aniracetam may also increase cholinergic transmission (Lee & Benfield, 1994; Schindler, Rush, & Fielding, 1984). This nootropic has shown potential for treating individuals with brain injuries, epilepsy, dementia (e.g. Alzheimer's), and neurodevelopmental disorders (e.g., Autism, ADHD, and Schizophrenia; Reynolds et al., 2017). It is sold as a pharmaceutical in Italy (Ampamet), China (Aniracetam-Sanhome, Bi Si Ling, Bo Bang Lin, San Le Xi, Shuntan and Yi Ling Shu), Greece (Memodrin, Referan) and by Pfizer in Argentina (Pergamid). Research investigating potential side effects of racetams notes no adverse side effects in animal studies (Gouliaev & Senning, 1994; Reynolds et al., 2017).

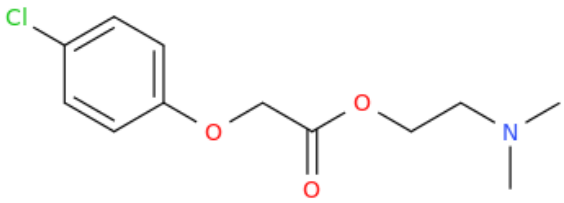
c) **Chemical analogy:** The opposite of benzodiazepines. Benzodiazepines are positive allosteric modulators of the general inhibitory neurotransmitter, GABA, and work by enhancing the natural effect of GABA at GABA receptor sites. Aniracetam is a positive allosteric modulator of the general excitatory neurotransmitter, glutamate, enhancing its effect at AMPA receptor sites.

d) **Case studies:** Nagasaka et al. (1997) reviewed two case studies of older adults (i.e. 72-year-old male and 68-year-old female) both with a diagnosis of progressive supranuclear palsy who were treated with Aniracetam to improve both cognitive (i.e. memory) and physical (i.e. walking) symptoms. There were no reported adverse side effects in these case studies (Nagasaka et al., 1997). Similarly, a case study of three females who had dementia and were using Aniracetam to treat symptoms reported no adverse side effects (Mizuki et al, 1984).

e) **Reported psychological side effects:** There were seven consumer experience reports identified for Aniracetam. Reports of psychological side effects were limited for Aniracetam. One consumer reported that the nootropic caused them to have a change in mood that was described as more "*energising rather than calming*" (Reddit Consumer), however did not explicitly state feelings of anxiety. Another reported consuming Aniracetam to assist with their symptoms of ADHD and experienced symptoms of mild depression (e.g., *"I've been a little depressed"*; Reddit Consumer). Cognitive effects such as brain fog, confusion, and incoherence were also noted.

f) **Other reported side effects:** Consumers reported sleeping deficits, build-up of tolerance, headaches, and fluctuating libido. Given that Aniracetam is a positive allosteric modulator of glutamate, it could be expected that this would be counter-indicated for individuals susceptible to seizures and for other conditions with dysregulation of glutamate, including schizophrenia.

Centrophenoxine



a) **IUPAC name:** 2-Dimethylaminoethyl (4-chlorophenoxy) acetate.

b) **Description:** Centrophenoxine, also known as meclofenoxate, is made from the amino acids dimethylamine-ethanol (DMAE) and p-chlorophenoxyacetic acid (Nandy & Bourne, 1966). It is sold as a pharmaceutical in Japan (Lucidril, Meclosert), Taiwan (Lisu) and Egypt (Lucudrul, Luciforte). In these cases, the drug is marketed as a treatment for cognitive impairment associated with ageing or strokes (PubChem, 15 August, 2018). It has variously been considered to assist in slowing the process of neuronal sentence (i.e. the process of gradual deterioration because of ageing; Riga & Riga, 1974). Nagy and Semsei (1983) noted that Centrophenoxine has shown to increase actions that facilitate slower degradation of neurons (i.e. glucose and oxygen absorption).

c) **Chemical analogy:** Choline or acetylcholine. Meclofenoxate has been studied as a cholinergic enhancer and increases production of choline which is also available for conversion into acetylcholine (National Center For Advancing Translational Sciences, 15 August, 2018).

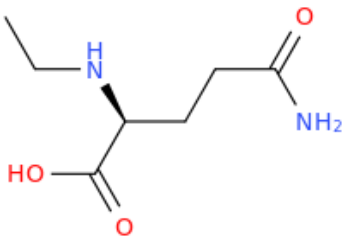
d) **Case studies:** To the authors knowledge no case studies have been published on Centrophenoxine. In published trials of the drug, no adverse effects were reported among older adults (Oliver & Restell, 1967). In a study exploring the effectiveness of Meclofenoxate in the treatment of tardive dyskinesia,

participants reported marked increases in parkinsonism movements (Izumi et al., 1986).

e) **Reported psychological side effects:** There were five consumer experience reports identified for Centrophenoxine. Of the limited consumer reports available for Centrophenoxine, few made mention of any mental health side effects. One consumer reported that there was a notable increase in irritability (e.g., *"I became easy irritated by small things"*; Reddit Consumer), while another consumer indicated feeling depressed (e.g., *"Centrophenoxine make me depressed"* Drug-forum Consumer).

f) **Other reported side effects:** Consumers reported heart burn, sleeping difficulties, and withdrawal (e.g., *"I get really, really tired when it wears off"* Reddit Consumer). Given that Centrophenoxine increases choline levels in the central nervous system, this will interact with other acetylcholine enhancing medications such as those used in dementia; and will interact with acetylcholine inhibitors such as anticholinergics.

L-theanine



a) **IUPAC name:** (2*S*)-2-Ammonio-5-(ethylamino)-5-oxopentanoate or *N*-Ethyl-L-glutamine.

b) **Description:** Theanine is an amino acid that has been identified in green tea leaves (Kahathuduwa et al., 2018). There are two chiral forms of theanine, but the majority of research has been conducted on the *levo* enantiomer (L-theanine; National Centre for Advancing translational Sciences, 12 August, 2018). Interest in this nootropic has arisen due to its potential to increase cognitive performance (e.g., alertness and attention; Kahathuduwa et al., 2018). Additionally, there have been some indications of its potential to be a relaxing agent (Kimura, Ozeki, Juneja, & Ohira, 2007; Ogawa, Ota, Ogura, Kato, & Kunugi, 2017). L-theanine's mechanism of action is by blocking certain acids (i.e. L-glutamic acid) to receptors (i.e. glutamate) (Kimura Et al., 2007).

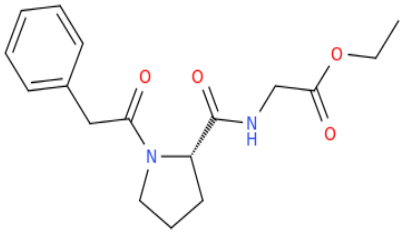
c) **Chemical analogy:** Anxiolytic by reducing excitatory neurotransmission. Theanine is structurally similar to glutamate and as such demonstrates binding at glutamate sites. It acts as an antagonist at AMPA and kainite glutamate receptors and as a weak agonist at the glutaminergic NMDA receptors (Nasiroleslami, & Mohitmafi, 2015; Nathan, Gary & Oliver, 2006). In animal studies this also appears to produce some enhancement in serotonin, dopamine and GABA activity (Nathan et al, 2006).

d) **Case studies:** To the authors knowledge no case studies have been published on L-theanine. A review of L-theanine by the Japan Food Additives Association indicated no adverse side effects related to L-theanine (Juneja, Chu, Okubo, Nagato, & Yokogoshi, 1999). The US Food and Drug Administration has granted L-theanine 'Generally Recognised as Safe' status. The European Food Safety Authority (2011) have published a scientific opinion statement that there is insufficient evidence for companies to claim improvement in cognition, reductions in stress, or improvement in sleep associated with L-theanine (PubChem, 12 August, 2018).

e) **Reported psychological effect:** There were 16 consumer experience reports identified for L-theanine. Consumers found it difficult to relax and experienced greater anxiety (e.g., *"anxiety spikes which then causes me to lose sleep"*; Reddit Consumer). Additionally, consumers reported decreased mood (e.g., *"I've noticed every time I take it I get depressed all day"*; Reddit Consumer), and irritability (e.g., *"It makes me grumpy"*; Reddit Consumer). Consumers also reported feeling disorientated and having lower concentration when taking L-theanine.

f) **Other reported side effects:** Consumers reported decreased energy, difficulty regulating bowel movements (e.g., *"I'm experiencing bad side effects diarrhea and constipation"*; Reddit Consumer), sleeping deficits, increased sweating, dizziness, and decreased libido (e.g., *"It made my penis stop working after two weeks of regular use"*; Reddit Consumer). Additionally, consumers reported addictive traits (e.g., *"I realise this drug can get very addicting"* Drugs-forum Consumer).

Noopept



a) **IUPAC name:** N-phenylacetyl-l-prolyglycine ethyl ester

b) **Description:** Noopept is the trade name for omberacetam, patented in both the US and Russia. It aims to stimulate broad areas of the brain to improve memory and learning (Kolbaev, Aleksandrova, Sharonova, & Skrebitsky, 2018). These substances have been used to potentially help individuals with dementia (e.g., Alzheimer's and Parkinson's) and mild cognitive impairments following physical trauma (e.g., traumatic brain lesions; Kolbaev et al., 2018). Animal studies have suggested that noopept may protect against neuron damage through inhibition of excessive calcium and from oxidative damage, and also block key components of cellular apototosis (Ostrovskaya, et al, 2014). Rodent models have also suggested increases in the neuroprotective Brain Derived Neurotrophic Factor (BDNF) (Ostrovskaya et al, 2008).

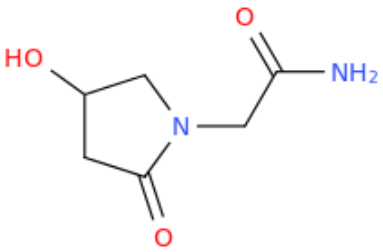
c) **Chemical analogy:** While the mechanism of action is as yet unconfirmed, possibly the best available analogy would be of enhanced recovery from cellular injury from inflammatory or free radical processes (National Centre for Advancing Translational Sciences,15 August, 2018; PubChem, 15 August, 2018).

d) **Case studies:** To the author's knowledge no case studies have been published on Noopept.

e) **Reported psychological effect:** There were three consumer experience reports identified for Noopept. Two consumers reported feeling anxious (e.g., *"It made me feel pretty tweaky and anxious"*; Reddit Consumer). There were also reports of cognitive difficulty (e.g., *"My head began to just crash. I felt like a hungover drunk with maybe a little high mixed in, but it was just awful"*; Drugs-forum Consumer).

f) **Other reported side effect:** Consumers reported physical pain (e.g., *"muscle/joint stiffness"*; Reddit Consumer) and decreased energy (e.g., *"I was getting more exhausted/drained towards the end of the day"*; Reddit Consumer).

Oxiracetam



a) **IUPAC name:** (*RS*)-2-(4-hydroxy-2-oxopyrrolidin-1-yl) acetamide.

b) **Description:** Oxiracetam is a racetam described as a new nootropic that aims to regulate rates of glutamate and cholinergic transmission and additionally enhance cerebral glucose levels particularly in the hippocampus (Hu, Shi, Xiong, Li, Fang, & Feng 2017; Marchi, Besana, & Raiteri, 1990). Oxiracetam has been used to help with memory and learning difficulties, particularly for individuals with vascular dementia (Hu et al., 2017).

c) **Chemical analogy:** As Oxiracetam is a racetam its chemical analogy is the same as Aniracetam and has been related in structure to nootropics such as Aniracetam, Phenylpiracetam, and Pramiracetam. As such it is the opposite of benzodiazepines. Benzodiazepines are positive allosteric modulators of the general inhibitory neurotransmitter, GABA, and work by enhancing the natural effect of GABA at GABA receptor sites. Oxiracetam is a positive allosteric modulator of the general excitatory neurotransmitter, glutamate, enhancing its effect at AMPA receptor sites.

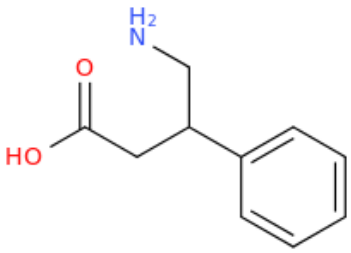
d) **Case studies:** Gou, Peng, and Ynag (2018) present a case study of an 84-year-old who consumed Oxiracetam with the packaging still intact. The adverse side effect (i.e. damage to the small intestine) experienced was attributed to the

packing being intact rather than Oxiracetam (Gou et al., 2018). No other case studies were revealed.

e) **Reported psychological effect:** There were five consumer experience reports identified for Oxiracetam. Consumers indicated a decrease in cognitive ability (e.g., brain fog, short term memory deficits, and forgetfulness). One consumer reported a decline in cognitive ability and an increase in anxiety symptoms (e.g., *"This shit scared the fuck out of me; brain fog, anxiety, short-term memory problems etc plagued me for three days straight and I thought I lost any form of higher order thinking"*; Reddit Consumer). Another consumer indicated a mild change in mood (e.g., *"slightly more irritable*; Drugs-forum Consumer).

f) **Other reported effects:** Other than the psychological side effects, consumers reported limited effects for Oxiracetam. One consumer indicated low energy (e.g., *"I was quite jittery and very forgetful, couldn't get myself to do anything";* Reddit Consumer).

Phenibut



a) **IUPAC name:** 4-Amino-3-phenylbutanoic acid.

b) **Description:** 4-amino-3-phenylbutyric acid (Phenibut) is a nootropic that is a derivative of gamma-aminobutyric acid (GABA; Joshi, Friend, Jimenez, & Steiger, 2017). It is licenced as a pharmaceutical in some countries (Drugs.com, 20 august, 2018): in China (An Luo, Change Rui, Hui You, Kai Luo, Li Sheng Bei Fen, Lu Bi An, Sheng Mai Fu, Ti Ta Ding, Tu Ti, Tuo Tai, Wei Ding, Xin Nuo Shu, Yi An Fen, Yi Hui Luo, Zhu Zhong Xin); Thailand (Bainto); Argentina (Butineuron); Egypt (Gaba); Japan (Gammalon); Brazil (Gammar), and Russia (Phenibut). It has been used to help individuals with alcohol withdrawal, sleep disorders (e.g., insomnia), and anxiety (Joshi et al., 2017).

c) **Chemical analogy:** Baclofen. Because Phenibut is structurally very similar to GABA it can act as a GABA analogue, binding at similar locations, particularly the GABAb receptor sites. Baclofen, a medication used in muscular disorders and increasingly in alcohol dependence, works as an agonist at the GABAb sites as well. As such, this drug acts as a CNS depressant, with motor relaxing, sleep enhancing and anxiolytic effects.

d) **Case studies:** Sankary, Canino, and Jackson (2017) described a case of a 25-year-old male who presented to the emergency room after a concerned friend noted abnormal behaviours (i.e. acting erratically, confusion, and what appeared

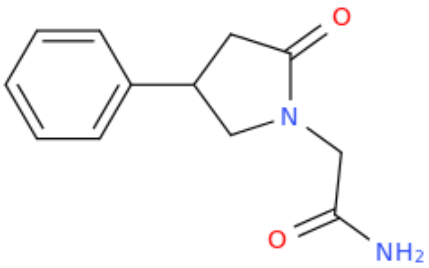
to be seizures). The man had ingested Phenibut he purchased online shortly before these symptoms appeared. Sankary et al. (2017) noted that Phenibut was likely the cause of symptoms, however this was unable to be confirmed due to adequate blood tests not being readily available to emergency rooms. Another case involved a 20-year-old female who presented to the emergency room with increased levels of confusion and delirium (Downes et al., 2015). It was established that she had consumed Phenibut that she had purchased online (Downes et al., 2015). Brunner, Healtheast, and Paul (2017) noted a case where an individual was admitted to the emergency room due to withdrawal symptoms that were later determined to be a result of Phenibut dependence. Although limited information was given, it was reported by Brunner et al. (2017) that this case is an example of why Phenibut should not be readily available and regulation guidelines should be explored more thoroughly, so recommendations can be made in regard to dependence. A 25-year-old man who was found unconscious on the floor of his apartment by a friend had reportedly been using Phenibut purchased on the internet for four days (O'Connell, Scheir, Hwang, & Cantrell, 2014). Samokhvalov, Paton-Gay, and Balchand (2013) reported a case of a 35-year-old male IT specialist who had purchased Phenibut to self-medicate his anxiety symptoms. The man presented with concerns regarding not being able to stop taking the Phenibut due to withdrawal symptoms (i.e. increased anxiety, low mood, and irritability) and required medical advice (Samokhvalov et al., 2013). The man was prescribed Baclofen to taper off the Phenibut use (Samokhvalov et al., 2013). It was reported that after nine weeks the man was able to stop using Phenibut without experiencing further withdrawal symptoms.

As previously mentioned in the introduction of this paper, Wong et al. (2015) described a 43-year-old male who had consumed Phenibut, who presented to the emergency room with increased agitation and involuntary muscle contractions. Due to the severity of his symptoms he had to be stabilised in the intensive care unit. All case studies involving Phenibut indicated a gap in identifying Phenibut as the cause of symptoms due to insufficient screening tools and clinical research explaining the reason behind the experienced symptoms (Downes et al., 2015; O'connell, et al., 2014; Samokhvalov et al., 2013; Sankary et al., 2017; Wong et al., 2015). In addition to formal case study's a media article mentioned in the introduction of this paper reported a group of Australian school-age children who were hospitalised as a result of dizziness and nausea related to consuming Phenibut (McNeilage, 2018).

e) **Reported psychological effect:** There were limited consumer reports indicating psychological side effects. Two consumers indicated an increase in anxiety, with one also indicating additional changes in mood (e.g., *"The anxiety occurs mostly from the overwhelming sensory stimuli… rebound anxiety and irritability"*; Whirlpool Consumer).

f) **Other reported effects:** Consumers reported impaired vision, nausea, and increased hunger. Consumers also indicated addictive properties leading to experiences such as withdrawal (e.g., *"Nasty withdrawal effects. Therefore, I am very careful about how often I use it and also my dosage when I use it"*; Drugs-forum Consumer), and identified it as dangerous (e.g., *"It's very similar in effect to alcohol and xanax. I consider it more of a drug than a noot"*; Reddit Consumer).

Phenylpiracetam



a) **IUPAC name:** (*R,S*)-2-(2-oxo-4-phenylpyrrolidin-1-yl)acetamide.

b) **Description**: Phenylpiracetam (also sold as Fonturacetam, Carphedon, Karfedon, Carphedone, and 4-phenylpiractam), is structurally similar to other drugs in the racetam family. Phenylpiracetam is another racetam that aims to increase cognitive ability, originally used to increase cognitive capacity of Soviet space crews (Veinberg et al., 2015). Phenylpiracetam's pharmacological nature is described as similar to other racetams (i.e. glutamate cholinergic transmission; Lee & Benfield, 1994), however additionally has an anticonvulsant action (Bobkov, Morozov, Glozman, Nerobkova, & Zhmurenko, 1983). Like other racetams, this nootropic has been used to assist individuals with traumatic brain injury, stroke, and dementia (Veinberg et al., 2015).

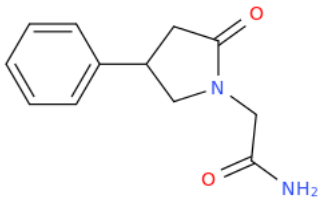
c) **Chemical analogy:** As Phenylpiracetam is a racetam, its chemical analogy is the same as Aniracetam and has been related in structure to nootropics such as Aniracetam, Oxiracetam, and Pramiracetam. As such it is the opposite of benzodiazepines. Benzodiazepines are positive allosteric modulators of the general inhibitory neurotransmitter, GABA, and work by enhancing the natural effect of GABA at GABA receptor sites. Oxiracetam is a positive allosteric modulator of the general excitatory neurotransmitter, glutamate, enhancing its effect at AMPA receptor sites.

d) **Case studies:** To the authors knowledge no case studies have been published on Phenylpiracetam.

e) **Reported psychological effects:** There were four consumer experience reports identified for Phenylpiracetam. Limited psychological effects were noted by consumers. One review indicated anxiety as a result of Phenylpiracetam, while another indicated cognitive decline (e.g., *"had brain fog for the following few hours"*; Reddit Consumer).

f) **Other reported side effects:** Consumers reported sleep deficits, headaches, and physical discomfort (e.g., *"I developed a headache, which is hard to say how much was the drug I didn't die obviously or need to go to a hospital, and by the next day the negative effects had worn off"*; Reddit Consumer).

Pramiracetam



a) **IUPAC name:** *N*-[2-(Diisopropylamino) ethyl]-2-(2-oxopyrrolidin-1-yl) acetamide.

b) **Description:** Pramiracetam is another racetam that has been noted to increase learning and memory, and additionally protect neurons (Angeles, et al.,2018). It is also known as amacetam, pramiracetamum, neupramir, and ectapram (PubChem, 21 August, 2018). An investigation into the chemical nature of Pramiracetam revealed similar regulation of glutamate and cholinergic transmission as other racetams, with specific release in the corpus stratum and cerebral cortex (Pugsley, Shih, Coughenour, & Stewart, 1983). This nootropic is also identified as potentially useful for individuals with dementia (e.g., Alzheimer's and frontotemporal dementia), epilepsy, partial seizures, and anxiety (Angeles et al., 2018).

c) **Chemical analogy:** As Pramiracetam is a racetam its chemical analogy is the same as Aniracetam and has been related in structure to nootropics such as Aniracetam, Oxiracetam, and Phenylpiracetam. As such it is the opposite of benzodiazepines. Benzodiazepines are positive allosteric modulators of the general inhibitory neurotransmitter, GABA, and work by enhancing the natural effect of GABA at GABA receptor sites. Oxiracetam is a positive allosteric modulator of the general excitatory neurotransmitter, glutamate, enhancing its effect at AMPA receptor sites.

d) **Case studies:** To the author's knowledge no case studies have been published on Pramiracetam.

e) **Reported psychological effects:** There were seven consumer experience reports identified for Pramiracetam. Consumer reports identifying side effects were limited for Pramiracetam, however there was one report of mood changes (e.g., *"Makes me really depressed and lethargic after chronic use";* Reddit Consumer). Interestingly, one consumer reported difficulty controlling affect (e.g., *"I was so into my own thought that I have been making facial expressions ... I tried to stop but I just couldn't help but react, I was mostly just smiling and nodding to a few good ideas I had"*; Reddit Consumer).

f) **Other reported effects:** Consumers reported physical pain (e.g., *"Pramiracetam can cause burns in the mouth";* Reddit Consumer) and headaches. One consumer identified addictive properties in relation to quickly building tolerance.

Preliminary Discussion

The 12-month monitoring revealed a variety of nootropics available to the Australian consumer. Of these identified nootropics, the top ten most common substances were examined in more detail by reviewing consumer reports on online forums. Study 2 gathered information to identify the chemical structure, a brief description, chemical analogy, published case studies, and reported side effects of each nootropic in the top ten most common nootropics identified. Through this exploration of consumer reports, the current study found instances where individuals experienced adverse mental health side effects as a result of using these nootropics. The current study did not obtain information regarding the prevalence of each nootropics use, and future research is needed to substantiate these consumer reported experiences.

Previous findings have indicated both mental health and physical side effects for various nootropics (Nelson & Lenton, 2017; Ragan et al., 2012; Talih & Ajaltouni 2015; Wong et al., 2015). The narrative review of nootropic consumer reports further supports these findings. Regarding psychological side effects, consumers reported low mood (e.g., depression), an increase in anxiety, irritability, and cognitive decline (e.g., brain fog). However, whether these side effects were due to the respective nootropic consumption is still unclear. Consumers also reported a range of other side effects such as physical pain (e.g., headaches), sleep disturbances, and addictive experiences (e.g., withdrawal and tolerance symptoms). Often consumers would indicate that when negative side effects arose, they would decrease the dose of nootropic, often informed by other consumer reports, with varying levels of success. Similarly, consumers often reported increasing the dose of nootropic if the desired cognitive benefit was not achieved. This was concerning and commonplace, with many consumers indicating this pattern of nootropic consumption. The findings from the consumer reports further

support the hypothesis that nootropics have harmful side effects and require structured research to more accurately inform consumers of their risk and benefit.

A review of case studies revealed concerning cases of nootropic risk. Particularly, case studies that involved Phenibut revealed the potential dangers of taking substances purchased online. These cases highlighted the need for nootropics to undergo the four-phase clinical trial process to ensure safety for consumers. In addition to further testing, the nootropics available to consumers need to be regulated in regard to their manufacturing to ensure safety. The Good Manufacturing Practice (GMP; Australian Government Department of Health, 2017) outlines policies and procedures to ensure products contain the right amount of advertised substances. Nootropics that contain variable rates of substance due to poor manufacturing would present greater risk to the consumer. The analogues approach only provided a general guide to substances that are similar in their mechanism of action. However, it revealed some similar medications (e.g. Modafinil and Baclofen) have well documented adverse outcomes for consumers. In the case of Phenibut, Baclofen were found to be a potential analogue as a result of Phenibut's interaction with GABA. Although the effect appears on a smaller scale, taking a large amount of Phenibut may have similar outcomes as Baclofen and therefore poses similar risk. These risks need to be explored by future research in order to ensure the safety of consumers. The common racetam drugs identified (e.g., Aniracetam, Oxiracetam, and Phenylpiracetam), appeared to have less reported negative side effects through both chemical analogy and case studies. It is possible that these nootropics pose less risk to consumers, however further research is required to identify possible side effects and safe dosages for these nootropics to be considered safe and therefore sellable to an online marketplace.

Several limitations of the current study are related to the method of gathering information solely from consumer reports. As displayed in the method, consumer reports ranged in the amount of detail provided and the approach to individual's reports (see Figures 7 and 8). In some cases, the consumer would detail the amount of the nootropic they were taking, whereas other consumers did not report this information. This limits the study's ability to investigate at what amount a certain nootropic had adverse side effects. Similarly, difficulty was found when consumers did not report individual information regarding weight, height, and age, which may have impacted the function of these nootropics. Another key challenge in generalising these results is that often consumers did not indicate whether and what other substances there were using, that may have impacted or compounded the reported side effects. The current study recognises these limitations and does not claim the reported side effects experienced were a result of the nootropic used. This research aims to provide this information as a foundation base, where consumer reports of side effects informs more structured future research.

Study 2 has provided a snapshot of psychological and other side effects of the top ten most common nootropics available to the Australian consumer, as experienced and reported by consumers. The current study adds to the growing body of literature regarding nootropics and provides a foundation for future research. Due to the variety of available nootropics and their increasing popularity, particularly for university students, clinicians should be aware of the potential side effects consumers may experience when using common nootropics. Additionally, as the literature grows in this area, it will be useful to have an understanding of potential for interactions with other medications and recreational substances.

Discussion

The current two-part study aimed to firstly monitor the nootropic online market over a 12-month period, identifying vendors and nootropics available to the Australian consumer. From the monitoring conducted, Adrafinil, Alpha GPC, Aniracetam, Noopept, Oxiracetam, Phenibut, Centrophenoxine, L-theanine, Phenylpiracetam and Paramiracetam were identified as the ten most common nootropics. The monitoring had several limitations associated with ambiguity of whether restricted substances were still obtainable to Australian consumers. Furthermore, substances were not tested to confirm if they were in fact the nootropic advertised. Despite these limitations, the monitoring successfully observed nootropics available to the Australian consumer over a 12-month period. Overall, the results indicated a stable market for nootropics.

Focusing on the top ten nootropics, the second study provided a review of consumers experiences posted on public forums. Consistent with previous research (Ragan et al., 2012; Talih & Ajaltouni 2015; Wong et al., 2015; Nelson & Lenton, 2017), several psychological and other side effects were reported by consumers, highlighting the potential adverse side effects of nootropics. As previously mentioned, the second study was limited in that the information reviewed was in the form of consumer reports and therefore identifying a direct link with side effects and nootropic use was not possible. With these limitations in mind, the current study aimed to provide an overview of side effects experienced and reported by consumers, to stimulate future research with a focus on enhanced scientific methods.

In its entirety, the current study holds several clinical implications that will be useful for consumers and mental health clinicians treating nootropic consumers. An understanding of available common nootropics and their associated side effects as

experienced by consumers will add to treatment considerations. For example if a client is consuming a nootropic purchased for perceived cognitive benefits they may have exacerbated mental health symptoms (e.g. anxiety and depression) that need to be considered for diagnosis and treatment. With the growing nootropic market and prevalence of their use, it is important to understand these new substances and how they may affect individuals (e.g. possible physical and mental health side effects, interactions with other substances, and other possible risks).

The consumer reports indicated that individuals using nootropics are experiencing adverse psychological side effects and therefore, may seek help from a clinician. Clinicians will need to understand the potential side effects of these nootropics, so they can effectively educate clients of the potential harms to their physical and mental health. Although this study focuses on nootropics available to the Australian consumer, these substances are also available internationally and therefore this information may be of use to clinicians outside of Australia. The study highlights the importance for clinicians to maintain up to date knowledge on non-prescription medication that may have an adverse effect for their clients who consume them. The current study has presented consumer reports and therefore, the information should be examined with caution and be used to inform possible areas for future research.

Future research is needed to further explore the side effects of nootropics, as knowledge of potential harms is crucial for both consumers and clinicians. The current study did not focus on the reported positive experiences of nootropic consumers. Future research exploring the effects of nootropics on improving cognitive performance in human samples would allow consumers to have an informed understanding of the

efficacy of nootropic use. In addition to informing clinicians of negative effects, identifying harms can be used to inform policy change regarding nootropics.

This study shows that a substantially sized, online nootropic market is available to the Australian consumer. Cumulatively, vendors have a variety of nootropic substances available for purchase and delivery to Australia. Although some nootropics are restricted in Australia, they are still available for purchase online, and if passed through Australian Customs, are accessible to consumers. A growing body of consumer reports for common nootropics exists, many of which indicate adverse side effects to be cautious of. Both clinicians and policy makers should be aware of nootropics and aim to appropriately inform and caution consumers of their potential harmful effects.

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Appendix A

Nootropic Internet Forums Examined for Search Terms

1. www.reddit.com/r/Nootropics
2. www.4chandata.org/fit/NOOTROPICS-THREAD
3. www.drugs-forum.com/forums/nootropics
4. www.nootropicsexpert.com/community-forum
5. www.whirlpool.net.au
6. www.longecity.org/forum
7. www.neuronootropic.com
8. www.anabolicminds.com
9. https://piracetam.net/forum/
10. www.excelmale.com/

Appendix B

Search Terms Tested

1. Smart Drugs
2. Nootropics Australia
3. modafinil
4. Nootropic
5. Noot
6. Alpha Brain
7. Cognitive Enhancer
8. Racetams
9. L-theanine
10. Theanine
11. Creatine
12. Bacopa Monnieri
13. Ashwaganda
14. Chaga
15. NSI-189
16. NDRI
17. Bacopa
18. Noopept
19. Semax
20. Vyvanse
21. Adderall
22. cognitive drugs
23. Alpha Brain
24. Onit
25. Ginkgo Biloba
26. Rhodiola Rosea
27. Siberian Ginseng